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A STUDY OF VASOMOTOR REFLEXES ELICITED BY HEAT AND COLD FROM REGIONS DEVOID OF TEMPERATURE SENSIBILITY (IN AN UNUSUAL CASE OF POST-TYPHOIDAL NEURITIS)*

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This study was undertaken with two objects: one clinical, the other physiological. From both aspects the results obtained seem to be of sufficient interest and utility to warrant their publication. The clinical object was primarily to throw light, if possible, on the diagnosis of a case which seemed to present considerable difficulty and concerning which very different conclusions had been arrived at by competent clinical observers. The physiological object was to contribute something to the solution of the question whether the afferent fibers through which the vasomotor reflexes induced by the application to the skin of heat and cold are identical with the fibers concerned in the corresponding sensations, a question which, so far as we are aware, has not received a definite answer. It is, of course, known that actual consciousness of the sensations is not necessary for the development of the vasomotor reactions, since they occur also in sleep. But we do not know whether a lesion, especially a peripheral lesion, which completely blocks the transmission of impulses along the nerves of temperature sensation, or at least prevents them from rising to the threshold value necessary for the production of sensation, blocks at the same time all the afferent vasomotor impulses set up by heat or cold. An answer to this question is not only of physiological interest, but also might, in certain cases, prove of diagnostic importance, particularly in affording a basis for an objective test of the existence and possibly for an objective measure of the acuity of temperature sensibility.

The vasomotor reflexes in this study were investigated by means of the method of measuring the blood-flow, previously described by one of

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us.[1] The reflexes elicited in one hand when the other hand or a portion of it is placed in cold or warm water, that is to say, the contralateral vaso-motor reflexes, were preferred for this study to the ipsolateral reflexes induced in the hand immersed in the hot or cold water, since it

TABLE 1.—RESULTS OF CALORIMETER TESTS ON R. E.

April 26, 1912. R. E. Hands in bath at 1:51½ p. m. Hands in calorimeters at 2:03 p. m. 3,015 c.c. water in each. Examination made in hospital.

Time	R.	L.	Notes	Time	L.	Notes
2.02	31.00	30.76		2.42	30.99	
2.04	30.91	30.69	Room 24.5 C.	2.43	31.025	
2.05	30.90	30.67		2.44	31.05	Room 24.0 C.
2.06	30.88	30.65		2.45	31.095	
2.07	30.86	30.63		2.46	31.12	Here cold water was brought into
2.08	30.84	30.63		2.47	31.13	room and excited his appre-
2.10	30.82	30.61	Room 24.3.			hensions.
2.11	30.80	30.59		2.48	31.15	At 2.48 right hand and wrist put
2.13	30.78	30.57		2.49	31.17	into water at 8 C. He feels it
2.15	30.77	30.555	Room 24.25 C.	2.50	31.19	very cold on wrist, but not at
2.17	30.76	30.545		2.51	31.20	all on fingers. Feels fingers
2.19	30.75	30.55		2.52	31.205	somewhat numb.
2.21	30.77	30.59	Room 24.2 C.	2.53	31.21	
2.22	30.775	30.605		2.54	31.215	
2.23	30.78	30.61		2.55	31.215	Still feels the right wrist very
2.24	30.79	30.635				cold.
2.25	30.795	30.655		2.56	31.22	The cold water is now at 12.5 C.
2.26	30.80	30.675		2.57	31.215	Room 23.6 C.
2.27	30.805	30.70		2.58	31.225	
2.28	30.81	30.725	Room 24.0 C.	2.59	31.225	
2.29	30.82	30.73		3.00	31.23	
2.30	30.83	30.745		3.01	31.235	
2.31	30.84	30.765		3.02	31.24	Room 23.6 C.
2.32	30.86	30.79		3.03	31.25	At 3.03 right hand and wrist put
2.33	30.875	30.825		3.04	31.255	into water at 43 C. The wrist
2.34	30.885	30.835	Right hand and wrist put in	3.05	31.27	still felt cold for a little time in
2.35	.....	30.85	water at 43 C. Feels it	3.06	31.29	the warm water.
			on wrist.	3.07	31.305	
2.36	.....	30.865		3.08	31.32	
2.37	.....	30.875		3.09	31.325	
2.38	.....	30.895		3.10	31.325	
2.39	.....	30.915		3.11	31.325	
2.40	.....	30.93		3.12	31.325	At 3.12 took hand out of calori-
2.41	.....	30.965				meter.
				3.25½	31.17	The right hand is reddish; ob-
						viously fair vasodilatation. Tem-
						perature of R. 30.395 C.

Cooling of R. 0.49° in 51½ minutes. Cooling of L. 0.155° in 13½ minutes. Volume of right hand 379 c.c., of left 397 c.c. Rectal temperature 37.05 C.

is commonly stated that even in the absence of connection with the central nervous system the blood-vessels quickly regain the power of responding to local changes of temperature through the intervention of a local

1. Heart, 1911, iii, 33, 76; THE ARCHIVES INT. MED., 1912, ix, 706.

regulating mechanism. Thus Trotter and Davies,[2] who studied the phenomena following the section of cutaneous nerves in themselves, state that "The vasomotor changes which follow nerve-section begin to show a diminution within a few days of the operation, and by the end of six weeks scarcely any abnormality of this function can be detected. It seems probable, therefore, that recovery occurs by some local compensatory mechanism rather than by an active regeneration of the vasomotor nerve fibers."

TABLE 2.—RESULTS OF CALORIMETER TESTS ON R. E.

May 2, 1912, R. E. Hands in bath at 3.15 p. m. Hands in calorimeters at 3.26 p. m. Mouth temperature 36.57 C. Temperature of arterial blood at wrist (say) 36.6 C. Examination made in hospital.

Time	R	L	Notes	Time	R	Notes
3.24½	31.10	31.16		3.45	31.235	At 3.43 left wrist withdrawn. He
3.27	31.07	31.15		3.46	31.27	feels warmth only on middle phal-
3.28	31.09	31.16	Room 25.5 C.	3.47	31.305	anx of left index finger. Hand kept
3.29	31.095	31.17		3.48	31.345	thus for the rest of the experiment.
3.30	31.105	31.185		3.49	31.395	Room 24.9 C.
3.31	31.105	31.20	Room 25.4 C.	3.50	31.41	At 3.50 left hand put in cold water
3.32	31.11	31.21		3.51	31.45	at 8.3 C. Wrist not immersed.
3.33	31.11	31.225				Only feels cold on middle phalanx
3.34	31.12	31.225				of index finger.
3.35	31.125	31.23		3.52	31.47	Room 25.0 C.
3.36	31.125	31.23		3.53	31.48	Still feels cold intensely on middle
3.37	31.135	31.225	At 3.37 left hand put in	3.54	31.495	phalanx of index. The cold water
3.38	31.13	.....	water at 43 C. Room			is now at 10.4 C.
			25.4 C. He feels warmth	3.55	31.505	Still complains of cold in this
			on wrist.	3.56	31.52	phalanx.
3.40	31.14	.....	At 3.40 withdrew wrist,	3.57	31.525	
3.41	31.15	.....	dried it, and put in cloth	3.58	31.535	Hands out at 3.58.
3.42	31.155	.....	to keep it from vessel.	4.09	31.425	Temp. of L. is now 30.95 C.
3.43	31.175	.....	Now feels warmth only			
3.44	31.195	.....	on middle phalanx of left			
			index finger. At 3.42 left			
			wrist immersed. He feels			
			it warm.			

Cooling of calorimeters R. 0.11° in 11 minutes. L. 0.275° in 32 minutes. Volume of right hand, 361 c.c.; left hand, 385 c.c. Pulse 76 (half reclining).

REPORT OF CASE

History.—The patient first came under observation of one of us in 1898, when he showed very marked atrophy of the small muscles of the hands, with less atrophy of the extensor group of the forearms and legs. He was not under close observation then until 1908, when the following history and condition were elicited:

R. E., white, aged 44 years, widower, laborer.

Family History.—Father died at the age of 37 of "paralysis of the brain." Mother died at the age of 30 of "childbirth." Three sisters and three brothers

2. Trotter and Davies: Jour. Physiol., 1909, xxxviii, 188.

dead; four died when very small; one died of typhoid fever and one died as the result of an accident. One uncle died of tuberculosis. Grandfather died of "liver trouble."

Previous History.—The patient had scarlet fever, measles, and mumps when small; had typhoid fever twenty-four years ago (in 1884), rheumatism in left shoulder two or three years previous to examination, and again a slight recurrence in the right leg during the previous seven months. The patient denies ever having had any venereal disease; had much catarrh sixteen years previously; could not smell anything unless very strong for the previous ten years. Had cough and expectoration for the previous five or six years. Tubercle bacilli were found in the sputum twice. He had pleurisy several times two or three years prior to examination, and was short of breath for five or six years; ankles swollen some six years previously; appetite only fair, some vomiting after eating for the previous year or so; pain in stomach at times—cramp-like, yet not very sharp; bowels regular; no incontinence of feces; some incontinence of urine eight or nine months previously that lasted for three months; had had no incontinence lately, no slowness in urination, and no change in sexual function. The patient experienced unsteadiness in the dark for twenty years; also when he closed his eyes to wash his face. There was some double vision for previous six years; no paresthesia. Wasting of hands, arms and legs, first noticed about the knees followed typhoid fever twenty-four years previously. He noted loss of sensation in hands, then in feet three or four years after he noticed the muscular wasting. He had fourteen operations for empyema of the frontal sinuses. When he had typhoid fever he had pain in the right groin; no bed sores; hair came out; noted much muscular wasting while sick; could not walk for three months after getting over his typhoid; had no pain in legs or arms at that time. Wasting of muscles was very marked three years after typhoid and about this time he noted loss of sensation, first in the lower legs, then in the feet, and then in the arms and hands. Feet numb; no stinging or burning. At this time the urine and sputum showed nothing abnormal.

Physical Examination.—This showed scars over the frontal sinuses from repeated operation, which interfered with the action of the frontal muscles; no pupillary reaction to ordinary light; no nystagmus; some contraction of the field of vision in all diameters; jaw-jerk not present; no glandular enlargement, no changes in the bones or joints; no scars or pigmentation of the skin.

Muscular System.—Quite marked atrophy of the trapezii, supraspinati and also of the serratus magnus on the right side; some wasting of the serratus magnus on the left. Both erector spinae muscles rather small and wasted. Considerable strength in the biceps, triceps and deltoid on both sides; also of the supinators and pronators; very marked atrophy of all of the small muscles of the hands and extensors and flexors of the forearm. Ulnar border of forearms concave due to muscular atrophy. Marked atrophy of the thenar and hypothenar eminences. He could not "make a fist" with either hand and had practically no grip. The face had a somewhat mask-like appearance, probably due to the sinus operations. He had a double partial ptosis (due to a sinus operations?); was able to shut both eyes; there seemed to be no paralysis of the facial muscles and the orbicularis oris was strong. The muscles of the soft palate and tongue were normal. The voice was husky, more like a voice of weakness than of paralysis. Platysma myoides and sternocleidomastoid and other muscles of the neck were much atrophied. The pectoral muscles showed good volume. The abdominal muscles were greatly weakened so that he could not bring himself into a sitting position without the aid of his arms. The atrophy was more marked on the left side. There was considerable wasting of all groups of muscles of the thigh, especially the abductors; marked atrophy of the peroneal groups, causing toe-drop; fairly good power in the calf muscles; extensors and flexors practically without power; marked wasting of the interossei; had some flat-foot.

Reflexes.—Bicipital, elbow and wrist-jerks all absent. Abdominal reflex present at all levels; cremasteric absent. Knee-jerks and Achilles-jerk absent on

TABLE 3.—RESULTS OF CALORIMETER TESTS ON R. E.

May 8, 1912. R. E. He says he feels better and is in better spirits than at the two previous examinations, partly due to the fact that his wife accompanied him; also to the expectation of some pecuniary reward. Examination made in laboratory. Hands in bath at 1.43 p. m., in calorimeters at 1.53 p. m.; 3,015 c.c. in each. Mouth temp. 36.95 C.

FIRST PART OF TEST

Time	R	L	Notes	Time	R	L	Notes
1.52	30.995	30.97	Room 22.2 C.	2.01	31.01	31.04	
1.54	30.935	30.925		2.02	31.025	31.05	Room 22.9 C.
1.55	30.935	30.93		2.03	31.04	31.065	
1.56	30.935	30.93		2.04	31.065	31.095	
1.57	30.96	30.955	Room 22.7 C.	2.05	31.095	31.125	Room 23.0 C.
1.58	30.98	30.99		2.06	31.11	31.14	
1.59	30.995	31.01		2.07	31.13	31.165	
2.00	31.00	31.025		2.08	31.15	31.20	

SECOND PART OF TEST

Time	L	Notes	Time	L	Notes
2.09	31.205	At 2.08 right hand put in water at	2.39	31.71	
2.10	31.22	43 C. Wrist not immersed. He	2.40	31.725	At 2.40½ right hand put in water
2.11	31.23	does not feel warmth at all.	2.41	31.735	at 8 degrees. Wrist carefully dried
2.12	31.235	Room 22.8 C.	2.42	31.74	and not immersed. He did not feel
2.13	31.25	The warm water is now at 41 C.	2.43	31.75	the cold at all.
2.14	31.26		2.44	31.765	Room 22.7.
2.15	31.295	Room 22.95 C.	2.45	31.78	
2.16	31.32		2.46	31.795	
2.17	31.325		2.47	31.805	The cold water is now at 9.7°.
2.18	31.33		2.48	31.81	
2.19	31.34		2.49	31.825	
2.20	31.35	Room 22.9 C.	2.50	31.83	Room 22.6.
2.21	31.36		2.51	31.835	
2.22	31.38		2.52	31.835	
2.23	31.405		2.53	31.835	
2.24	31.425		2.54	31.84	At 2.54 right hand, including wrist,
2.25	31.435	Room 22.7 C.	2.55	31.84	put into water at 43°. He feels
2.26	31.45		2.56	31.84	the wrist warm.
2.27	31.47		2.57	31.84	Room 22.8.
2.28	31.495	At 2.28 right hand, including wrist,	2.58	31.84	
2.29	31.50	immersed in water at 43 C. Feels	2.59	31.845	
		it warm on wrist.	3.00	31.845	
2.30	31.525	Room 22.9 C.	3.01	31.85	
2.31	31.53		3.02	31.855	
2.32	31.54		3.03	31.855	
2.33	31.565		3.05	31.85	At 3.05 hand out of calorimeter.
2.34	31.59	Room 22.7 C.	3.13	31.74	Temp. of R. 30.39.
2.35	31.625				
2.36	31.635				
2.37	31.65				
2.38	31.685	Room 22.8 C.			

Cooling of calorimeter R. 0.76 degrees in 65 minutes; cooling of calorimeter L. 0.11 degrees in 8 minutes. Volume of right hand 403 c.c. Volume of left hand, 421 c.c.

both sides. No plantar reflex; no Babinski, Oppenheim or Gordon reflexes were present on the left side. There was a slight plantar reflex on the right side involving but the four small toes, and with this stimulus the quadriceps contracted although he felt nothing. No Babinski, Oppenheim or Gordon present on the right side; gluteal reflexes present; no enlargement or tenderness of the nerve trunks found.

Sensory Symptoms.—The patient was anesthetic to all forms of sensation over the frontal region laterally to the line of the outer canthus of the eyes, probably due to nerve lesions caused by sinus operations. No anesthesia of the rest of the face. No anesthesia of the neck or trunk. Toes, feet, and legs were anesthetic to all forms of sensation to above the knees. On the right side the line of anesthesia is just at the upper border of the patella and running around to one inch higher on the posterior surface. On the left leg the line of anesthesia was an inch above the patella in front, curving downward a little on each side, then curving up posteriorly to the upper part of the popliteal space. Analgesia extended to about two inches higher than anesthesia to touch in front and slightly lower posteriorly. Deep pressure sense was absent in the legs.

Left arm, hand and fingers were anesthetic to all forms of sensation from a line about three-fourths inch above elbow-joint.

Right arm, hand, and fingers were anesthetic to all forms of sensation, including deep pressure, below a line about one and one-half inches above the condyle of the humerus, extending a little higher on the anterior surface.

Stereognostic sense was gone in the hands; could not tell position of fingers or hand.

Patient stood with knees over-extended and walked with steppage gait, throwing right foot farther forward, however, than left. Toes had a tendency to drag, due to drop-foot.

Lumbar puncture showed low pressure, clear fluid; twelve cells, mostly lymphocytes, to the c.mm. Urine showed nothing abnormal.

April 13, 1909, the patient showed slight nystagmus; contrary to what was previously observed pupils equal and reacted to light and accommodation. Seemingly some weakness of the labial muscles and cheek muscles. Tongue showed wrinkling and thinning, seemingly slight atrophy, equal on both sides. Some difficulty in swallowing owing to the food coming out of the nose.

He said he could not walk down hill, but must run down owing to weakness of the extensors of the legs. At this time both patellar and both plantar reflexes were absent.

April, 1912, blood showed a negative Wassermann reaction.

May, 1912, patient again came under observation at the Cleveland City Hospital and a few additional facts in regard to the history may be added.

The patient stated that he was in a sanatorium for tuberculosis seven years previously and was discharged as seemingly cured after nine months' stay. He gave no history of lightning pains or gastric crises. He still experienced considerable difficulty in walking. He had some trouble at times in controlling the bladder and had several involuntary bowel movements, but as a rule he had no trouble in controlling the sphincters of bladder and bowel.

He said his feet felt cold and numb at times, but he had no other subjective sensory symptoms.

He had lately married for the fourth time. History of his marital relations showed nothing suggestive of a syphilitic infection.

He believed that the strength in his hands and feet was slowly improving, which seems to be very certain judging from the records of former examinations. The patient said his hands and feet always felt cold to other people when he, himself, could tell no difference.

Examination of the chest showed evidence of a quiescent tuberculosis at the right apex. Cardiovascular system shows nothing abnormal, although heart sounds seem quite faint. No murmurs present.

TABLE 4.—RESULTS OF CALORIMETER TEST ON R. E.

May 18, 1912. R. E. He came from his home to the City Hospital for this examination. The weather was fairly warm. Hands in bath at 11:48 a. m. Hands in calorimeters at 11.58 a. m. 3,015 c.c. water in each. Mouth temperature, 36.55 C.

FIRST PART OF TEST

Time	R.	L.	Notes	Time	R.	L.	Notes
11.57½	30.91	30.87	Room 24.8 C.	12.09	30.99	30.985	
11.59	30.89	30.85		12.10	30.995	31.00	
12.00	30.90	30.86		12.11	31.00	31.02	Room 24.8 C.
12.01	30.91	30.88	Room 24.9 C.	12.12	31.01	31.025	
12.02	30.93	30.91	He saw cold water being	12.13	31.02	31.035	
12.03	30.94	30.92	prepared with ice.	12.14	31.035	31.045	Room 24.6 C.
12.04	30.94	30.925	Room 24.9 C.	12.15	31.045	31.055	
12.05	30.945	30.93		12.16	31.06	31.065	
12.06	30.96	30.94		12.17	31.065	31.08	At 12.17 right hand (not
12.07	30.97	30.955					wrist) put into water at
12.08	30.98	30.97	Room 24.9 C.				8.2 C. He did not feel
							the cold at all.

SECOND PART OF TEST

Time	L.	Notes	Time	L.	Notes
12.18	31.085		12.49	31,555	
12.19	31.09	Room 24.4 C.	12.50	31.575	At 12.50 immersed right hand over
12.20	31.10		12.51	31.58	wrist in the cold water. Feels it
12.21	31.11	Room 24.6 C.	12.52	31.59	very cold on wrist. The water is
12.22	31.125				8.9 C.
12.23	31.14		12.53	31.585	Room 24.6 C.
12.24	31.155	Room 24.5 C.	12.54	31.60	
12.25	31.17		12.55	31.61	Still feels it quite cold on wrist.
12.26	31.19		12.56	31.625	Room 24.6 C.
12.27	31.22		12.57	31.625	
12.28	31.23	Room 24.5 C.	12.58	31.625	
12.29	31.24	At 12.29 right hand (not wrist)	12.59	31.63	Room 24.7 C.
12.30	31.25	put into water at 43.5 C. Feels	1.00	31.63	
12.31	31.25	nothing. Room 24.7 C.	1.01	31.635	
12.32	31.27	The cold water is now 9.7 C.	1.02	31.64	At 1.02 right hand and wrist put
12.33	31.31		1.03	31.645	into water at 43.4 C. Feels it
12.34	31.325	Does not feel the warm water.	1.04	31.65	warm on wrist. Room 24.9 C.
12.35	31.34	Room 26.9 C.	1.05	31.67	
12.36	31.365		1.06	31.69	Room 24.9 C.
12.37	31.40		1.07	31.71	
12.38	31.42	Room 24.9 C.	1.08	31.72	
12.39	31.425		1.09	31.725	
12.40	31.435		1.10	31.73	Room 24.9 C.
12.41	31,445	The warm water is now 40 C.	1.11	31.73	
12.42	31.46	At 12.42 right hand (not wrist)	1.12	31.735	The warm water is now at 40.3 C.
12.43	31.485	put into water at 8 C. Does not	1.13	31.74	At 1.13 dried and wrapped up right
12.44	31.50	feel the cold at all.	1.14	31.75	hand.
12.45	31.515	Room 24.8 C.	1.15	31.755	
12.46	31.525		1.16	31.765	Room 24.9 C.
12.48	31.54		1.17	31.775	
			1.18	31.79	
			1.19	31.815	
			1.20	31.825	Room 24.9 C.
			1.21	31.835	At 1.21 hand removed from calori-
			1.29	31.76	meter. Temperature of R. is
					30.42 C. at 1.29.

Cooling of R. 0.64° in 72 minutes; L. 0.08° in 8 minutes. Volume of right hand, 391 c.c.; left hand, 409 c.c.

Abdomen showed nothing abnormal. Liver and spleen did not seem to be enlarged. Genitalia were normal.

Reflexes: Knee-jerks, Achilles-jerks, Babinski, Gordon and Oppenheim reflexes all absent on both sides. Marked wasting of about the same muscles that were atrophied at the time of examination made in 1908, and described above; although the atrophy did not seem to be as pronounced and the strength in the hands was much better.

Special Sense.—He could taste neither sweet, sour nor bitter on the anterior two-thirds of the tongue on both sides. On the posterior one-third of the tongue he seemed to be able, especially on the left side, to taste acid, but no sweet or bitter substances. Sense of smell was absent. Hearing and sight were normal.

Sensation.—There was loss to all forms of sensation (including sense of position, deep pressure and vibratory sense) in the right hand extending up on the forearm with a U-shaped boundary on the anterior surface and extending much higher on the posterior surface, but here also having an irregular boundary outline (Figs. 1 and 2). Just above this area of complete anesthesia to all forms of sensation there was an area extending almost to the elbow joint where

Fig. 1.—Anterior surface. Total anesthesia indicated by shading with small circles; hypesthesia (to all forms of sensation) by shading with small crosses.

all forms of sensation were present, but less acute than normal. The left hand with the exception of the entire index finger was anesthetic to all forms of sensation. (At the blood-flow examinations he stated positively that he felt heat and cold only on the middle phalanx of index finger.) The upper boundary of anesthesia of the hand was about as high as the so-called glove anesthesia. Above this area was a band about 5 inches wide where all forms of sensation were present, but less acute than normal. Above this band there was another area extending almost to the elbow joint where all forms of sensation were again absent.

The right foot and leg were anesthetic to all forms of sensation up to an irregular shaped line with its highest point three fingers' breadth below the patella. Posteriorly this line curves downward to a point six finger breadths below the level of the head of the fibula. Over this area all forms of sensation were lost, including muscle sense, deep pressure sense and vibratory sense. The left foot and leg showed almost identically the same area of anesthesia, with practically the same boundary, with the exception that there was a small round area about an inch in diameter on the sole of the foot just below the inner malleolus where pain sense seems to be present.

There was a sore on the plantar surface of the right big toe that seemed to be painful to touch. Patient thought it was caused by badly fitting shoes. It soon healed up perfectly. Numerous other abrasions due to shoes were not felt by the patient at all.

Marked displacement, laterally and in other direction, of the knees, ankles and toe joints was not perceived by the patient, but he seemed to appreciate the position of the left big toe.

It seemed as though vibratory sense was lost over the patella, fibula, tibia and bones of the feet. There seemed to be a lessening of the vibratory sense over the lower third of both thighs.

Blood Examination.—Blood examination showed 5,200,000 reds, 6,900 leukocytes and a negative Wassermann. Lumbar puncture showed rather low pressure (80 drops to the minute) clear, cell-count 4 per c mm.

X-ray examination of the chest and spine showed nothing abnormal.

Urine.—Specific gravity 1,018, trace of albumin; no sugar and no casts found.

Electrical Reaction.—Electrical reaction showed greater diminution in the faradic than in the galvanic irritability in the areas affected by atrophy and

Fig. 2.—Posterior surface. Shading same as in Fig. 1. Note the small circular area on the left sole which seems to be sensitive to pain.

anesthesia. Tested more exactly November 14, 1912, with a McIntosh battery (galvanic current from 25 cells with total voltage of 37. Faradic current from coil on the same apparatus actuated by two similar cells, No. 4 Columbia type 1½x4 inches in size connected in parallel). The patient stated that he could feel somewhat better on the hands and arms than at last examination, including heat and cold. Following are details of the electrical reactions:

RIGHT ARM. GALVANIC CURRENT (BROAD ELECTRODE ON BACK[3]

N. Medianus (7 cm. above wrist): KCC>ACC. No KOC. Little if any AOC.

M. Palmaris Longus: KCC fair. ACC slight. No KOC or AOC. (Fairly sharp pain at KC and some pain at AC.)

M. Supinator Longus (Palm of hand): KCC (good) >ACC, which >AOC. KCC>KOC. No contraction either with K or A at C or O. (Slight pricking pain at AC, AO and KC. None at KO.)

3. The "motor points" correspond to those given by Schatzsky (Allbutt's System of Medicine, i, 454). It is not implied that the position of the points was identical in our patient, nor that only the corresponding muscle or nerve was always stimulated by the current used.

TABLE 5.—SUMMARY OF RESULTS ON R. E.

Date	Temperature C. of				Vol. of Hand in c.c.		Heat Given Off in Small Calories			Blood Flow Gms. per Min.		Flow per 100 c.c. of Hand per Min.		Notes
	Room	R. Cal.	L. Cal.	Art. Bld.	R.	L.	R.	L.	In mins.	R.	L.	R.	L.	
April 26	24.0	30.82	30.69	36.6	379	397	951	1,469	15	12.19	18.41	3.21	4.56	For the 15 mins. preceding the vasomotor test.
	....	30.85	30.78	.....	...	...	459	598	6	14.78	19.02	3.90	4.71	For 6 mins. immediately preceding the vasomotor test.
	24.0	.....	30.88	.....	...	...	.....	444	6	.....	14.37	....	3.56	First 6 mins. immersion of right hand and wrist in warm water.
	....	.....	31.04	.....	...	...	.....	1,161	8	.....	29.00	....	7.19	Next 8 minutes.
	23.6	.....	31.18	.....	...	...	.....	287	3	.....	19.61	....	4.86	First 3 mins. with right hand and wrist in cold water.
	....	.....	31.22	.....	...	...	.....	636	12	.....	10.94	....	2.71	Next 12 minutes.
May 2	25.4	31.10	31.19	36.6	361	385	541	578	10	10.93	11.87	3.03	3.08	For 10 mins. before vasomotor test.
	25.4	31.14	.....	.....	...	...	237	.....	5	9.64	.....	2.67	....	First 5 mins. immersion of left hand in warm water.
	24.9	31.28	.....	.....	...	...	1,150	.....	8	30.02	.....	8.31	....	Next 8 minutes.
	25.0	31.44	.....	.....	...	...	271	.....	2	29.18	.....	8.08	....	First 2 mins. with left hand in cold water.
	....	31.55	.....	.....	...	...	423	.....	6	15.51	.....	4.29	....	Next 6 minutes.

May 8	22.9	31.04	31.06	36.95	403	421	1,213	1,407	12	19.00	22.12	4.71	5.25	For the 12 mins. preceding vasomotor test.
	22.9	.....	31.27	.....	...	...	.....	867	10	.....	16.96	....	4.03	First 10 mins. with only anesthetic part of right hand in warm water.
	22.8	.....	31.41	.....	...	...	.....	1,012	10	.....	20.29	....	4.82	Next 10 minutes.
	22.8	.....	31.52	.....	...	...	.....	329	4	.....	16.83	....	4.00	First 4 mins. immersion of right wrist also in warm water.
	22.8	.....	31.63	.....	...	...	.....	1,009	8	.....	26.33	....	6.25	Next 8 minutes.
	22.7	.....	31.78	.....	...	...	.....	686	8	.....	18.42	....	4.37	First 8 mins. immersion of anesthetic part only of right hand in cold water.
	22.7	.....	31.83	.....	...	...	.....	282	5	.....	12.24	....	2.90	Next 5 minutes.
	22.8	.....	31.85	.....	...	...	.....	460	9	.....	11.13	....	2.64	For 9 mins. immersion of right hand and wrist in warm water.
May 18	24.8	30.98	30.97	36.55	391	409	1,158	1,317	18	12.83	14.57	3.28	3.56	For 18 mins. preceding the vasomotor tests.
	24.8	31.02	31.02	.....	...	...	630	719	10	12.66	14.44	3.24	3.53	For the last 10 mins. of this period.
	24.6	.....	31.11	.....	...	...	.....	383	6	.....	13.04	....	3.19	First 6 mins. immersion of anesthetic part of right hand in cold water.
	24.6	.....	31.19	.....	...	...	.....	524	6	.....	18.10	....	4.42	Next 6 minutes.
	24.9	.....	31.35	.....	...	...	.....	1,146	13	.....	18.83	....	4.60	For 13 mins. during immersion of anesthetic part of right hand in warm water.
	24.8	.....	31.52	.....	...	...	.....	650	8	.....	17.94	....	4.38	For 8 mins. immersion of anesthetic part of right hand in cold water.
	24.7	.....	31.61	.....	...	...	.....	616	12	.....	11.54	....	2.82	For 12 mins. immersion right hand and wrist in cold water.
	24.9	.....	31.67	.....	...	...	.....	410	5	.....	18.67	....	4.56	For the first 5 mins. immersion of right hand and wrist in warm water.
	24.9	.....	31.73	.....	...	...	.....	308	6	.....	11.83	....	2.89	For the next 6 mins. of immersion in the warm water.
	24.9	.....	31.79	.....	...	...	.....	598	8	.....	17.44	....	4.26	For 8 mins. with right hand dried and wrapped up.

LEFT ARM. GALVANIC CURRENT (BROAD ELECTRODE ON BACK)

N. Medianus (7 cm. above wrist): KCC (flexion of three middle fingers) >KOC. (Feels pain distinctly.) ACC (slight flexion of two middle fingers) is slightly less than KCC. AOC slight or absent. (Pain greater at AC than at AO.)

M. Palmaris Longus: No contraction, and he only just feels it.

M. Supinator Longus: KCC (fair) >KOC. ACC about the same as KCC. AOC is nearly as strong as ACC and stronger than KOC. Almost the strongest current yielded by the battery is needed to obtain even KCC.

M. Biceps: KCC (good) >KOC. Contractions easily obtained with rheostat 2 to 3 divisions from the maximum. The contractions are better than those elicited with the active electrode over the point "N. medianus" (7 cm. above wrist) immediately after, the current intensity indicated on the milliamperemeter being practically the same.

M. Extensor Carpi Ulnaris, M. Extensor Digiti Minimi, M. Extensor Indicis, M. Extensor Digitorum Communis: Fair contraction, both KCC and ACC, with rheostat three divisions from the maximum. (Pain felt rather strongly.)

N. Medianus (above elbow): KCC. Good contraction (flexion of fingers) and considerable pain.

The flexion of the fingers is greater than KCC with N. medianus (7 cm. above the wrist), but there is much less difference between the effects of the galvanic current on the two points than between the effects of the faradic current. With the galvanic current pain is quite distinct at both points although stronger at the point above the elbow.

Palm of Hand: KCC, fair movement of fingers, KCO very slight. (Only dull pains at KC.) ACO, fair contraction and >ACC.

LEFT ARM. FARADIC CURRENT (BROAD ELECTRODE ON BACK)

N. Medianus (7 cm. above wrist): No contraction and very little sensation with shield one-third withdrawn. Some contraction with core completely uncovered by withdrawing shield entirely.

N. Medianus (above elbow): Good contraction (flexion of fingers) with core one-third uncovered and pain. Much stronger contraction with shield completely withdrawn than at the lower N. medianus point.

M. Palmaris Longus: Fair contraction with shield one-third withdrawn. The contraction is mainly proximal to the point.

M. Supinator Longus: Fair contraction with shield half withdrawn.

M. Biceps: Good contraction with weakest current (shield not withdrawn at all). He feels it well.

M. Extensor Carpi Ulnaris, M. Extensor Digiti Minimi, M. Extensor Indicis, M. Extensor Digitorum Communis: Contraction with shield one-fourth withdrawn. The contraction is mainly proximal to the points stimulated.

RIGHT ARM. FARADIC CURRENT (ONE ELECTRODE IN PALM)

N. Medianus (7 cm. above wrist): No contraction whatever with maximum strength. He feels some pain but not much.

M. Supinator Longus: With maximum strength some contraction (dorsiflexion of thumb, index and middle fingers). Pricking sensation mostly in the palm; only a little at position of the other electrode.

LEFT ARM. FARADIC CURRENT (ONE ELECTRODE IN PALM)

N. Medianus (7 cm. above wrist): With maximum strength some contraction of muscles of ball of thumb, etc.

M. Supinator Longus: Fair contraction with maximum strength.

M. Palmaris Longus: No contraction except with maximum strength, which gives fair flexion to fingers.

Four blood-flow experiments on as many separate days during a period of three weeks were made on the hands of this patient and one on his feet. The experiments on the feet will be reserved for inclusion in a separate paper on the blood-flow in the feet. A fifth experiment on the hands was partially vitiated for its immediate purpose by the fact that the man came to the laboratory on a rather cold morning with his hands uncovered. This caused a persistently diminished flow in the hands, as is particularly apt to be the case in persons with a habitually poor flow, so that the existence of reflex vasomotor effects from one hand to the other could not be studied under favorable conditions. Nevertheless, the results in this experiment, although quantitatively less marked, were qualitatively the same as in the others.

The question whether in this patient the efferent vasomotor path in the areas where sensation is entirely gone is still capable of conducting vasomotor impulses was studied in the experiments of April 26 and May 2, in which the vasomotor reflexes elicited in one hand by the application of heat or cold to sensitive areas on or near the other hand were determined. The reflex effects on the blood-flow were normal in direction and of considerable intensity.

Thus, in the experiment of April 26 the flow for a period of six minutes before the vasomotor reaction was tested, was 3.90 grams per 100 c.c. of hand per minute in the right hand, and 4.71 grams in the left. For a fifteen-minute period, immediately preceding the vasomotor test, the flows were, respectively, 3.21 and 4.56 grams. The flow in both hands was slowly increasing up to six or eight minutes before the test. The right hand, it will be remembered, is the weaker of the two, a condition which, in old-standing neuritis, has been found associated with a smaller flow. In neither hand is the flow of normal amount for the age of the patient, and the temperature of the room and calorimeters. This agrees entirely with the fact that his hands were always cold to the touch, although he himself did not know that they were cold. When the right hand was immersed in warm water so deeply that warmth was distinctly felt on the wrist, the flow in the left hand for the first six minutes of the immersion was reduced to 3.56 grams per 100 c.c. of hand. A rather abrupt increase then occurred, the average flow for a further period of immersion of eight minutes in the warm water being 7.19 grams per 100 c.c. of hand per minute. The initial diminution of the flow in the hand when the contralateral hand is immersed in warm water is the normal effect, only in this case the diminution is more prolonged than normal. On immersion of the right hand and wrist in cold water, which was well felt on the wrist, the flow in the left was diminished from the average of 7.19 grams per minute to 4.86 grams for the first three minutes and to 2.71 grams for the next twelve minutes, while the right hand continued

in the cold water. The vasoconstriction and vasodilatation in the left hand elicited by thermal stimuli applied to the right hand and appreciated only on the right wrist were therefore perfectly distinct.

In the experiment of May 2 the initial flows were 3.03 and 3.08 grams per 100 c.c. per minute for the right and left hands, respectively. When the left hand was immersed in warm water so that the sensation of warmth was only appreciated on the middle phalanx of the left index finger, although there quite intensely, a vasomotor reflex occurred in the contralateral hand with exactly the same features as in the experiment of April 26, viz., a longer initial period than usual, in which the flow was diminished by the application of warmth to the contralateral hand (from 3.03 to 2.67 grams per 100 c.c. per minute for a period of five minutes) succeeded by a very durable increase (to 8.31 grams per 100 c.c. per minute) for the remaining eight minutes, during which the left hand continued in the warm water. The reaction to the immersion of the left hand in cold water was also quite distinct (an eventual reduction of flow in the right hand from 8.31 to 4.29 grams per 100 c.c. per minute).

It is noteworthy, and of course, quite in accord with experimental facts, that a wide-spread and intense vasomotor reflex may be initiated from a very limited receptive area. Therefore, the intensity of the vasomotor reflex in those two experiments is no indication that any portion of the reflex has been elicited from the anesthetic areas of the hands immersed in the warm or cold water. We shall see, however, later on that even the anesthetic areas do contribute something to the total effect, although the contribution is relatively slight.

From these experiments it can be concluded (1) that the efferent vasomotor paths in the parts which are totally anesthetic in this patient are quite capable of conduction; (2) that the centers concerned in reflex vasomotor action on the blood-vessels of a totally anesthetic hand and elicited by heat and cold from areas on or near the anesthetic contralateral hand are quite permeable for vasomotor impulses.

The vasomotor reflex is so good that we can assume that practically the whole efferent vasomotor path to the hand is concerned in it. Therefore, when it is elicited from so limited a receptive surface the relatively small number of fibers in the afferent path must have free access either directly or through the bulbar vasomotor centers to the spinal cells of origin of the afferent fibers for practically the whole of the contralateral hand, not to speak of other areas which very probably are involved in the reaction. This could not well be the case if a lesion existed in the cord, and in the immediate vicinity of the cells of reception of the small afferent path, extensive enough to account for the sensory and motor deficiency in the hands. Assuming, then, that of the three links in the

vasomotor reflex arc, two (the efferent path and the central mechanism) are absolutely or relatively intact, we have now the means of determining the condition of the third link (the peripheral afferent path). This was done in the experiments of May 8 and May 18, in which the behavior of the reflexes in one hand when only the anesthetic parts of the contralateral hand were exposed to heat or cold were studied. It is there shown that the reflexes elicited from the anesthetic areas are feeble in comparison with those elicited from adjacent areas in which sensation is preserved. Thus, in the experiment of May 8 the initial flow in the left hand was 5.25 grams, in the right hand 4.71 grams per 100 c.c. per minute. For the first ten minutes of immersion of the anesthetic portions of the right hand in warm water the flow in the left hand was 4.03 grams per 100 c.c. per minute, which increased to 4.82 grams during continued immersion of the right hand (still only the anesthetic portions) for an additional period of ten minutes. Great care was taken that no part of the hand should be immersed in which the patient preserved any power whatever of temperature sensation. The wrist was carefully protected by cloths from contact with the vessel. When the wrist of the right hand as well as the anesthetic portions of the hand were immersed in warm water so that the patient experienced a distinct sensation of warmth on the wrist, the flow in the left hand, after an initial diminution from 4.82 grams to 4.0 grams per 100 c.c. per minute for a period of four minutes (the normal effect), increased to 6.25 grams during continued immersion of the hand and wrist in the warm water for an additional period of eight minutes. Immersion of the anesthetic part of the right hand in cold water caused the flow in the left hand to diminish to 4.37 grams for the first eight minutes of immersion. The rest of the experiment probably should not be used, as the marked diminution in the flow is a phenomenon often witnessed at the end of long experiments.

In the experiment of May 18 the initial flows were 3.28 and 3.56, respectively, for the right and left hand. Immersion of the right hand (only the anesthetic portions) in cold water caused the flow in the left hand to diminish from 3.56 to 3.19 grams for the first six minutes of immersion. During the next six minutes of immersion of the right hand in cold water the flow increased to 4.42 grams per 100 c.c. per minute, the increase, as is usually the case even in normal hands, beginning abruptly. On immersion of the anesthetic portions of the right hand in warm water a further small increase (to 4.60 grams per 100 c.c. per minute) occurred and this was sustained during the total period of immersion of the right hand in warm water thirteen minutes. Immersion of the anesthetic portions of the right hand in cold water now caused a slight diminution of the flow in the left hand (from 4.6 to 4.38 grams per 100 c.c. per minute for a period of eight minutes). Changes of a very

different order of magnitude were produced when the right hand including the wrist was now immersed in cold water, the flow in the left hand falling from 4.38 to 2.82 grams per 100 c.c. per minute for the twelve minutes of immersion. The patient felt the cold intensely on the right wrist, not at all on the rest of the hand. Immersion of the right hand and wrist in warm water caused an increase in the flow in the left hand from 2.82 grams to 4.56 grams per 100 c.c. per minute for a period of five minutes. During the next six minutes, while the right hand and wrist were still immersed in the warm water, the average flow in the left hand sank to 2.89 grams (probably vasoconstriction due to the great duration of the experiment). When the right hand was removed from the warm water, dried carefully and wrapped up in a cloth, the flow in the left hand rose again to 4.26 grams per 100 c.c. per minute.

DISCUSSION AND CONCLUSIONS

From these four experiments taken together the following conclusion seems justified: Since there is no conspicuous defect of conductivity either in the centers or in the efferent vasomotor paths as shown in the first two experiments, and incidentally also in the last two, the defect in the experiments in which only anesthetic areas were exposed to warmth or cold must lie in the afferent portion of the arc; that is to say, in the afferent path from the anesthetic regions through which vasomotor reactions in the contralateral hand can be normally elicited. Further, the lesion as regards the vasomotor path is in all probability a peripheral one involving mainly the afferent fibers and at a level at any rate distal to their cells of reception in the spinal gray matter. The suggestion is that the lesion in the other afferent paths is also peripheral, a question of diagnosis left in doubt by previous clinical examinations. This supports the diagnosis of the case as post-typhoidal neuritis of unusually long duration and with other unusual features.

Perhaps, roughly speaking, we might arrange the various paths as regards the severity of the peripheral lesion as follows: 1. Sensory, including tactile and thermal sensation, pain and also deep sensibility; for example, vibratory. 2. Afferent vasomotor. 3. Voluntary motor. 4. Efferent vasomotor. It is not implied that the whole change is necessarily in the peripheral fibers nor is it perhaps probable, but only that the peripheral fibers are mainly affected. The classification is purely functional. It is not implied, for instance, that Group 2 is anatomically distinct from Group 1. There is, of course, no inherent improbability in the supposition that the efferent and afferent portions of the vasomotor arc are differently affected. The distal neurons of the two paths belong to different anatomical systems, the efferent to the autonomic, the afferent to the cerebrospinal system.

While the changes in the flow in one hand produced by immersing the completely anesthetic portion of the contralateral hand in cold or warm water are not large in comparison with the changes elicited by the application of heat or cold to parts with good temperature sensibility, they seem sufficiently definite to permit the conclusion that even from a part completely anesthetic as regards temperature sensation (as well as regards the other forms of sensation) vasomotor reflexes can be evoked by cold or warmth. Two explanations might be thought of:

1. The block which conditions the anesthesia is partially central, i. e., somewhere above the entrance of the afferent fibers into the cord. In this case the afferent sensory paths from the anesthetic areas need not be looked on as totally incapable of conduction of sensory impulses and therefore not incapable of conducting impulses which can cause reflex vasomotor effects.

2. The peripheral block being complete for sensory impulses, it is still incomplete for afferent vasomotor impulses. The second condition might depend (a) on the possibility of the reception and conduction by the nerves of skin sensation (particularly in the case we are discussing the nerves which subserve the sensations of warmth and cold) of impulses which can affect reflex vasomotor centers even when they are incapable of receiving and conducting impulses which give rise to the sensations in question, or at least incapable of receiving and conducting them in sufficient intensity to reach threshold value; (b) on the possibility that other afferent fibers than those concerned in sensation exist in the peripheral nerves, through which impulses elicited by heat or cold may pass to vasomotor centers. If such fibers exist there is no reason why they should be involved in exactly the same degrees as the sensory fibers in a chronic peripheral pathological process which is nothing if not selective.

That it is not necessary to make the assumption involved in explanation 1 was shown by experiments on a surgical case in which a central lesion could be positively excluded. By an injury to the median nerve in the forearm, certain phalanges were rendered totally anesthetic to warmth, cold and the other forms of cutaneous sensation. A small, but distinct, reflex vasomotor effect on the contralateral hand was obtained on immersion of the anesthetic phalanges in warm or cold water. The subject, a medical student, thoroughly appreciated the object of the experiment, and his statement that during the immersion of the anesthetic phalanges no temperature sensation whatever was experienced, can be taken as strictly accurate. In this case then, the afferent vasomotor path from the anesthetic phalanges was already in some degree permeable when excited by heat or cold at a time when no thermal sensation had returned. As the case had not come under observation at an earlier date it is impossible to say whether the degree of conductivity observed was a

residual phenomenon due to the sparing of the path, or of a portion of it, in the original lesion, or to recovery. It is, of course, conceivable that impulses which can liberate vasomotor reflexes may be capable of being received by, and of passing up, regenerating nerve fibers at a much earlier period than impulses which give rise to sensations. This case is being further studied as regards the return of function by the subject himself under the direction of one of us and will form the basis of a separate paper. The question whether thermal vasomotor reflexes can be elicited from deeper structures than the skin, from muscles, for example, whose afferent fibers when electrically stimulated cause such marked vasomotor effects, has an obvious relation to this subject. We have not discussed it because we do not possess the data for doing so. In any case it is certain that the skin, which must bear the brunt of those changes in the external temperature, the adaptation to which is one of the great offices of the vasomotor mechanism, must be far more important in this regard. We have also made no allusion to the possibility that temperature changes, due either to direct conduction or to the passage of the blood from the submerged parts to neighboring parts not involved, or not involved in an equal degree in the lesion, may affect afferent nerves capable of liberating vasomotor reflexes, because if such changes occurred they were too slight or too gradual to elicit sensations of cold or warmth, and it was only with temperature changes which did this that we concerned ourselves.

VASOMOTOR REFLEXES ELICITED BY HEAT AND COLD FROM AREAS DEPRIVED OF TEMPERATURE SENSIBILITY BY A TRAUMATIC LESION *

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In a pathological case already reported in this journal[1] it was shown that vasomotor reflexes, small but definite, could be elicited by the application of heat or cold to areas totally devoid of temperature sensibility. The present communication establishes the same fact, for an otherwise normal subject, in whom anesthesia of certain portions of one hand had been caused by accidental injury to the median nerve in the fore-arm.

CASE REPORT

History.—The subject, O. C. W., is a healthy fourth-year medical student, aged 24. September 15, 1912, at 9:30 a. m., he injured his left arm by the breaking of a carboy full of water which he was carrying. The main wound was on the front of the lower part of the forearm. In addition there was a small wound on the dorsal aspect of the little finger. From the way in which the carboy was being held the tendons in the lower part of the forearm and at the wrist were on the stretch and stood out, so that they could easily be severed by a relatively superficial wound. The bleeding, so far as could be observed, was entirely venous and capillary. Certainly no large artery was cut. The hemorrhage was controlled by the patient himself by pressure around the wrist with the right hand until assistance was procured. He was taken to a hospital and under gas anesthesia eight flexor tendons which were found divided were sutured, and in addition the tendon of the extensor digiti quinti propius on the dorsum of the little finger. A careful search was made in the wound for divided nerves but no large nerve was found. The wound was closed and a splint put on the arm and hand. The arm was dressed morning and evening for the first few days and afterward each day, and healing occurred without complication.

During the interval (4½ hours) between the injury and the operation the patient was able to make the following observations.

Motor Changes.—Immediately after the accident it was impossible to flex either the thumb or the index finger or any of their phalanges, but adduction and abduction of the thumb and index were not impaired. The middle, ring and little fingers could be flexed, the deep tendons being intact. The hand could not be flexed on the wrist. The little finger could not be extended.

Sensory Changes.—The entire index finger became numb immediately. This numbness later involved more or less the whole of the hand, but was most marked on the radial side of the palmar aspect.

The patient continued from time to time to make observations.

September 20, 1912. The numbness, except on the index finger, has changed into an intense burning and tingling sensation which involves the thumb, middle finger, radial side of ring finger and the radial half of the palm. The little finger

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1. Stewart and Laffer: THE ARCHIVES INT. MED., 1913, xi, 365. (See preceding paper).

and the ulnar half of the palm are not involved in this sensation and the same is true of the dorsal, ulnar and palmar surfaces of the ring finger. The skin over the area involved in this sensation as well as that over the index finger is very dry. The furrows of the skin in this region are noticeably white. There is some swelling in the index and middle fingers.

September 30, 1912. The splint was removed to-day. The sensation of burning and tingling remains the same and is limited as above described. It is like the pain of a burn exposed to the air and is worse at night. The skin has the same appearance as before and is still very dry. On the palmar surface of the third phalanx of the middle finger a small area about 1 cm. in diameter can now be delimited which is very sensitive to light stroking (cotton wool or brush). This hypersensitive spot was first noticed in the latter part of the first week. This area and the rest of the phalanx are anesthetic as regards pain (pin prick), deep pressure, heat and cold. The anesthetic area (to touch, pain, pressure, heat and cold) involves the palmar surface of the thumb, the radial half of the palm, the palmar surface of the index and middle fingers and the entire periphery of the second and third phalanges of the index and middle fingers. The radial side of the ring finger has a certain degree of hypesthesia. The involved area is more or less sensitive to light stroking, the middle finger most, the index finger least. On the middle finger especially such stroking is quite painful while hard rubbing causes no pain. A mere touch on the middle finger, especially the palmar surface, caused discomfort, whereas prolonged stroking or (light) rubbing was necessary to produce the same sensation on the index finger. This hypersensitive condition appeared about the second week while the splint was still on. Sensation is normal on the dorsum of the thumb up to and around the nail, also on the dorsum of the first phalanx of the index and middle fingers. The sides of the first phalanx of the index and middle fingers are normal. The skin over the involved area is desquamating. Motion of the whole hand and of the fingers is greatly limited.

October 10, 1912. Motion much improved. Sensation the same as before, but the painful sensations are less intense. The palm and palmar surface of the middle finger are not so sensitive to light contact (stroking). Cannot localize contact. Cannot distinguish pressure at two points. Thermic sensation absent in the entire involved area.

October 20, 1912. Motion better. Can flex all fingers into the palm. Deep flexor tendon to index does not work, does not flex the terminal phalanx. Tactile sensibility is not appreciably improved. Localization and discrimination of the shape, etc., of a body touching the skin are absent.

November 10, 1912. Motion better. Otherwise no change.

December 10, 1912. Skin over the involved area not so dry. Obviously there is now some sweat secretion but still much less than on the normal skin. Occasional shooting pains starting about the wound and shooting to the ends of the index and middle fingers. On tapping lightly over the scar a sensation similar to that caused by a weak electric shock is transmitted to the ends of the index and middle fingers, never transmitted elsewhere.

December 19, 1912. Accidentally burnt the palmar surface of the terminal phalanx of the index finger. The finger was in contact with a radiator and the patient was quite unconscious it was being burnt. A large blister formed in about an hour.

December 20, 1912. The blister was opened and drained by puncturing with a needle through healthy skin at the side. It began to fill immediately and in a few minutes was as large as before. It was reopened and filled again very quickly and this process was repeated about fifteen times during the day.

December 21, 1912. The skin over the blister was cut off and the accumulation of liquid stopped at once. There was no recurrence of the formation of liquid. No pain was felt from the burn at any time. It was so deep as to involve the fat pad. By January 7, 1913, the burn was completely healed.

December 23, 1912. The distribution of sweat secretion and sensation was carefully tested in the laboratory.

Sweat Secretion.—There is no question that the area deficient in sweat secretion is much smaller than at first, or even than a month ago. The hand was wrapped in a towel after being wiped dry and put into a hot-air oven. The oven contained a dish of water to help to keep the air moist and thus hinder evaporation of the sweat. Sweat secretion is still small or absent over an area on the ball of the thumb about 3½ cm. long by 2 cm. broad. The edge of this area approaches the cleft between the thumb and index finger. On the rest of the radial portion of the palm and on the second and third phalanges of the middle finger, where sweating was absent before, it is now present to a certain extent.

Sensation, Radial Half of Palm.—The small area on the ball of the thumb in which sweat secretion is absent is totally insensitive to light touch (with blunt pencil point, cotton wool or brush). To pressure it is sensitive. If a blunt point is pressed down with more than a certain amount of force the pressure sensation goes on to definite though delayed pain sensation. This area is less sensitive to pressure than the rest of the ball of the thumb. With a tube containing water at 3 C. no cold sensation on this small area, but with a chip of ice a sensation of cold is obtained though delayed. No sensation of warmth with a tube containing water at 45 C., nor was there any effect for some distance outside the boundary. Hotter water (50 C.) is felt as warm on points just outside although not felt at all inside the boundary, whereas elsewhere on the palm it is felt as hot. The rest of the radial half of the palm is sensitive to touch (light contact of blunt point, light stroking with cotton or brush), pressure (with rubber pad of pencil), pain (pin-prick), heat and cold (chip of ice). While ice causes cold sensation everywhere on the palm of the hand it is somewhat less marked on the ball of the thumb and over the radial half of the palm than over the rest of the palm, rather a cool sensation than that of ice.

The thumb is sensitive to light touch but on the palmar surface of the second phalanx, although a tactile sensation is elicited, the subject cannot tell anything about the kind of body touching him; for example, whether it is pointed or not. Pressure sensation is fair on the palmar surface of the thumb and good on the dorsum. Ice gives no sensation of cold on the palmar surface of the second phalanx; elsewhere the normal sensation. The pin-prick, which elsewhere on the thumb causes pain, elicits only the sensation of contact on the palmar surface of the second phalanx.

The little finger is normal. The more detailed examination of the remaining three fingers follows.

Light Touch.—Index Finger, Palmar Surface.—On the second and third phalanges no sensation to simple touch but some sensation to pressure, not going on to pain even with strong pressure with a blunt point. On the first phalanx touch is felt but the shape of the object is not discriminated. *Dorsal Surface.*—Third phalanx only slight sensation of touch without discrimination of nature of object. Second phalanx much better touch sensation. First phalanx normal. *Ulnar Surface.*—Third phalanx no tactile sensation. Second phalanx fair, third normal. *Radial surface.*—Third phalanx poor tactile sensation, second pretty good, first normal.

Middle Finger.—Hyperesthetic to light touch on palmar aspect, elsewhere much the same as the index.

Light stroking with cotton wool or brush shows much the same distribution of anesthesia over the whole involved area as in the other tests.

Cold.—Index, Palmar Surface.—Second and third phalanges no cold sensation to ice. First phalanx, little if any cold sensation, perhaps a slight sensation after a long application of the ice. *Dorsal and Radial Surfaces.*—Second and third phalanges no cold sensation. First phalanx normal. *Ulnar Surface.*—Second and third phalanges, no cold sensation. First phalanx, cold sensation but delayed.

Middle Finger, Palmar Surface.—No cold sensation on any of the phalanges, but the contact of ice gave a sensation of touch on all. *Dorsal, Radial and Ulnar Surfaces.*—Second and third phalanges, no cold sensation; first phalanx normal.

Ring Finger.—Palmar, dorsal and ulnar surfaces normal. *Radial Surface.*—First and third phalanges normal; a small area about 5 mm. distal to the joint between the first and second phalanges on the radial side and overlapping the dorsal surface of the second phalanx either gives no cold sensation with ice or the sensation is markedly delayed.

The application of a point of ice to the point on the scar in the forearm, mechanical stimulation (tapping) of which gives a sensation like a weak electric shock running down to the index and middle fingers causes no effect except a local sensation of cold over the point touched. On no part of the anesthetic area is anything except a local sensation of cold obtained on contact with ice. No "peripheral reference" of cold[2] could be demonstrated at this stage at any part of the anesthetic area.

Warmth (warm tube).—Index Finger, Palmar Surface.—No sensation of warmth on any phalanx. Sensation of contact on first phalanx. *Dorsal Surface.*—Warmth felt on first phalanx, nothing on second and third.

Middle Finger.—The same portions are sensitive to warmth as to cold and in about the same degree.

Ring Finger.—Normal except the small area on the second phalanx which was insensitive to ice. This area gives the sensation of warmth with a tube which elsewhere gives a hot sensation.

Pain (pin-prick).—Index Finger, Palmar Surface.—Only sensation of contact is given on first phalanx except with considerable pressure, when pain is elicited. Second and third phalanges give only sensation of contact to pin-prick and heavy pressure is required to elicit even this. No discrimination of the nature of the object. *Dorsal Surface.*—First phalanx normal. Second phalanx greater pressure of the pin needed to give pain than on normal skin. Third phalanx no pain, even with considerable pressure; only an indefinite contact sensation.

Middle Finger, Palmar Surface.—All the phalanges are hyperesthetic. A pin-prick gives definite pain, much more intense than on the rest of the skin. Second and third phalanges are more sensitive than the first. Light contact or a light prick gives most pain. Pressing or rubbing hard with a flat surface does not give pain, nor does pinching. Light stroking gives a sensation of exaggerated tickling which is almost pain.

Ring Finger.—Normal to pin-prick except the small area which is abnormal to temperature sensation. On this area a pin-prick gives sensation of contact and not of pain.

Pressure (with rubber pad of pencil).—Index, Palmar Surface.—First phalanx, fair sensation, diminishing on second phalanx toward third phalanx. *Dorsal Surface.*—First phalanx normal. On third phalanx pressure sensation is barely obtainable. Second phalanx intermediate.

Middle Finger, Palmar Surface.—Good pressure sensation on all phalanges but accompanied with tingling. *Dorsal Surface.*—First phalanx normal. Second phalanx fair sensation, and better than on second phalanx of index finger. Third phalanx about the same as second phalanx of index finger; on increasing the pressure the pressure sensation goes on to pain, which is not the case on the second and third phalanges of the index finger.

Ring Finger.—Normal everywhere.

January 21, 1913. Light touch (stroking with brush) is felt over the whole of the involved area but only slightly on the second and third phalanges of the index finger. On the palmar surface of the middle finger the sensation is one of exaggerated tickling. No area can now be found on the ball of the thumb which is insensitive to contact (brush or blunt pencil point). The radial portion of the palm is moist although dryer than the rest of the palm.

2. Trotter and Davies: Jour. Physiol., 1909, xxxviii, 178.

January 24, 1913. Peripheral reference of cold cannot be obtained. Sensation of cold over the scar is delayed.

The subject came under observation of the senior author for the first time, a month after receiving the injury. The first blood-flow examination was made Oct. 15, 1912.

October 15, 1912. The blood flow and vasomotor reflexes of the hands were examined after the subject's day's work as a medical student. Pulse 112 (sitting). Hands in bath at 4:12 p. m. Hands in calorimeters at 4:35 p. m. The hands were kept in the bath for a longer time than usual owing to accidental

TABLE 1.—Calorimetric Tests of Blood-Flow in Hands of O. C. W.

Time.	R.	L.	Notes.
4:34	31.02	31.10	
4:36	31.02	31.10	
4:37	31.04	31.12	
4:38	31.07	31.15	Room 22.6 C.
4:39	31.10	31.19	
4:40	31.13	31.22	Room 22.6 C.
4:41	31.20	31.26	
4:42	31.25	31.31	Room 22.5 C.
4:43	31.31	31.34	
4:44	31.38	31.39	
4:45	31.42	31.43	Room 22.8 C.
4:46	31.46	31.46	
4:47	31.495	31.495	
4:48	31.52	31.52	
4:49	31.535	31.53	
4:50	31.56	31.55	Room 22.9 C.
4:51	31.56	31.56	
4:52	31.585	31.57	Room 22.9 C.
4:53	31.595	31.585	† *
4:54	31.595		Room 22.9 C.
4:55	31.61		
4:56	31.65		
4:57	31.69		Room 23.1 C.
4:58	31.71		
4:59	31.73		Room 23.1 C.
5:00	31.785		
5:01	31.81		Room 23.0 C.
5:02	31.825		At 5:02 anesthetic phalanges immersed in water at 43.4 C.
5:03	31.845		
5:04	31.89		
5:05	31.91		
5:06	31.96		
5:07	32.01		
5:08	32.08		
5:09	32.11		
5:10	32.16		At 5:10 whole left hand put into water at 42.6 C.
5:11	32.18		Room 23.3 C.
5:12	32.22		
5.13	42,265		
5:14	32.29		
5:15	32.335		
5:16	32.395		
5:17	32.45		
5:18	32.48		At 5:18 whole left hand put into cold water.
5:19	32.495		Room 23.4 C.
5:20	32.505		
5:21	32.535		Felt the cold water sharply
5:22	32.57		at first but is now getting
5:23	32.59		used to it.
5:24	32.60		Room 23.35 C.
5:25	32.61		
5:26	32.625		Hands out of calorimeter at 5:26.
5:38	32.46		Temp. of L. is now 31.04 C.
....	.....		Cooling of R. 0.165 degrees in 12 minutes.
....	.....		Cooling of L. 0.545 degrees in 45 minutes.

† At 4:53 the anesthetic phalanges of left hand immersed in water at 8.2 C.

* The hands were cautiously immersed so that the subject should not feel the cold water, the hand and wrist being kept from contact with the vessel by a towel. On their first introduction into the cold water the anesthetic phalanges were immersed for a moment rather too deeply, so that he felt what he termed a suspicion of cold. The fingers were at once withdrawn a little and thereafter he had no sensation of cold whatever.

delay in the preparations: 3,015 c.c. of water in each calorimeter. Volume of right hand 447 c.c., of left 436 c.c. Rectal temperature 37.15 C. Height 5 feet, 7½ inches. Weight 146 pounds. Came in from street not wearing gloves.

In this experiment immersion of the anesthetic phalanges of the left hand in cold water caused a definite though transient diminution of the flow in the right hand (from 7.39 to 3.82 grams per 100 c.c. per minute) for the first two minutes of immersion. For the next seven minutes

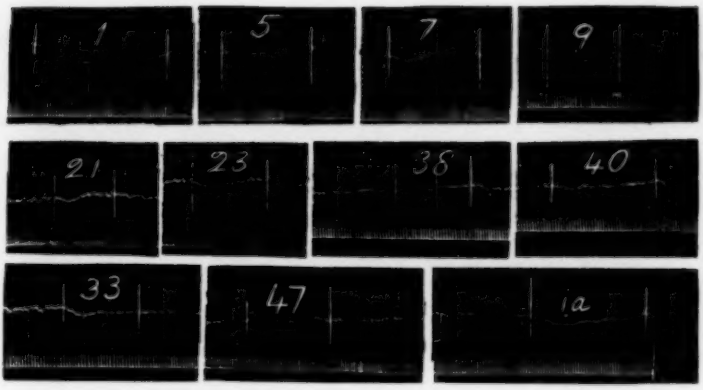
while the anesthetic phalanges continued in the cold water the flow increased to 7.58 grams. For the whole nine minutes the flow was diminished from 7.39 to 6.75 grams per 100 c.c. of hand per minute. The initial flow in the left hand was somewhat less than that in the right (6.83 grams per 100 c.c. per minute). A considerable and more persistant increase in flow followed the immersion of the anesthetic phalanges

TABLE 2.—CALORIMETRIC TESTS OF BLOOD-FLOW IN HANDS OF O. C. W.

Time.	R.	L.	Notes.
2:11	30.93	30.90	Room 23.1 C.
2:13	30.89	30.93	
2:14	30.93	30.99	Room 23. 3 C.
2:15	30.99	31.04	
2:16	31.06	31.10	Room 23.3 C.
2:17	31.12	31.16	
2:18	31.195	31.205	Room 23.3 C.
2:19	31.265	31.265	Room 23.3 C.
2:20	31.31	31.31	
2:21	31.36	31.34	Room 23.2 C.
2:22	31.40	31.39	Room 23.3 C.
2:23	31.44	31.41	At 2:23 anesthetic phalanges put into water at 8 C.

Time.	R.	Notes.
2:24	31.46	
2:25	31.48	Room 23.3 C.
2:26	31.515	
2:27	31.55	Room 23.3 C.
2:28	31.59	
2:29	31.63	Room 23.2 C.
2:30	31.69	Room 23.3 C.
2:31	31.73	
2:32	31.78	Room 23.3 C.
2:33	31.805	At 2:33 anesthetic phalanges put into water at 43.5 C.
2:34	31.825	
2:35	31.85	
2:36	31.89	
2:37	31.92	
2:39	31.96	Room 23.4 C.
2:39	31.99	
2:40	32.04	
2:41	32.08	Room 23.4 C.
2:42	32.115	
2:43	32.16	Room 23.3 C.
2:44	32.195	At 2:44 whole left hand put in water at 43 C. Room 23.3 C.
2:45	32.32	
2:46	32.265	
2:47	32.30	
2:48	32.355	Room 23.3 C.
2:49	32.395	
2:50	32.44	Room 23.3 C.
2:51	32.51	
2:52	32.57	Room 23.3 C.
2:53	32.61	
2:54	32.67	
2:55	32.705	At 2:55 whole left hand put in water at 8 C.
2:56	32.74	Room 23.1 C.
2:57	32.775	
2:58	32.795	
2:59	32.825	
3:00	32.85	
3:01	32.875	Room 23.3 C.
3:02	32.895	
3:03	32.895	
3:04	32.90	At 3:04 dried and wrapped left hand in warm cloth. Room 23.3 C.
3:05	32.91	
3:06	32.925	
3:07	32.935	Room 23.1 C. He says the left hand feels warm.
3:08	32.955	
3:09	32.97	
3:10	32.975	
3:11	32.975	Room 23.3 C.
3:12	33.02	Hand removed from calorimeter at 3:12.
3:28	32.86	Temp. of L. is now 30.695 C.
....	.....	Cooling of R. 0.16 degrees in 16 minutes.
....	.....	Cooling of L. 0.715 degrees in 65 minutes.
....	.....	Vol. of right hand 431 c.c.
....	.....	Vol. of left hand 407 c.c.
....	.....	Rectal temperature 37.05 C.

in the warm water (from 7.58 to 10.58 grams per 100 c.c. of hand per minute for a period of eight minutes). When the whole left hand was now immersed in the warm water some further increase in the flow of the right hand (to 11.14 grams per 100 c.c. per minute for a period of eight minutes) ensued, and this was promptly cut down to 7.24 grams when the whole left hand was immersed in the cold water. Not only was the diminution greater when the whole hand was immersed, but it was



Description of Figure 1.—Finger plethysmograph tracings. The tracings are to be read from left to right. The periods of immersion of the parts to which cold or warm water was applied are indicated by the vertical lines drawn through the curves. The signal trace which marked the moment of immersion and withdrawal has been omitted. Time is marked in seconds.

1. Right middle finger of S., a normal man, in plethysmograph. Left hand in cold water (8 C.) for the period comprised by the vertical lines drawn through the curve. The shrinking of the finger (fall of the curve) is evident.

5. Right middle finger of W. in plethysmograph. Whole left hand in cold water (8 C.).

7. Right middle finger of W. in plethysmograph. The anesthetic phalanges of left hand in cold water (8 C.).

9. Right middle finger of S. in plethysmograph. Distal half of left hand in cold water (8 C.).

21. Right middle finger of W. in plethysmograph. Anesthetic phalanges of left hand in warm water (45 C.).

23. Right middle finger of W. in plethysmograph. Second and third phalanges of ring, and third phalanx of little finger of left hand in warm water (45 C.).

33. Right middle finger of W. in plethysmograph. The anesthetic phalanges of left hand in cold water (8 C.).

38. Right index finger of W. in plethysmograph. Anesthetic phalanges of left hand in warm water (43 C.).

40. Right index finger of W. in plethysmograph. Second and third phalanges of ring finger and third phalanx of little finger of left hand in warm water (43 C.).

47. Second and third phalanges of left index finger of W. in plethysmograph. Whole right hand in cold water (6.5 C.).

1-a. Right middle finger of W. in plethysmograph. The anesthetic phalanges of left hand in cold water (6.9 C.). This was the first immersion of the phalanges.

also more persistent than when the anesthetic phalanges alone were exposed to the cold water.

After an interval of two months another examination was made.

December 19, 1912. Tested thermal sensibility of left hand before the experiment. No sensation to immersion in warm or cold water on middle finger, at least up to the upper third of the second phalanx. On the index finger no sensation on immersion at least up to a level well above the second interphalangeal joint. A perfectly safe level of immersion was thus determined beforehand. An hour before he had burned the flexor surface of the third phalanx of the index finger on a radiator without knowing it and there was a blister on it. He washed his hands in warm water before they were put into the bath at 2 p. m. Pulse 104 (sitting). Hands in calorimeter at 2:12. In testing, the anesthetic phalanges were passed through a hole in a thick plate of cork to avoid contact of sensitive skin with the vessel or water.

TABLE 3.—Experiment 3 with Right Hand in Calorimeter.

December 21, 1912. Right hand put into bath at 11:18 a. m. Left hand in air. Pulse 104 (sitting). At 11:28½ right hand put into calorimeter.

Time.	R.	Notes.
11:28	30.60	
11:29	30.53	Room 22.7 C.
11:30	30.54	Room 22.9 C.
11:31	30.57	
11:32	30.625	Room 22.9 C.
11:33	30.69	
11:34	30.75	Room 22.9 C.
11:35	30.795	
11:36	30.855	
11:37	30.91	
11:38	30.97	Room 22.9 C.
11:39	31.02	
11:40	31.07	At 11:40 anesthetic phalanges put in water at 8.1 C. No sensation.
11:41	31.095	Room 22.9 C.
11:42	31.12	
11:43	31.165	Room 23 C.
11:44	31.205	
11:45	31.25	Room 22.8 C.
11:46	31.305	
11:47	31.365	Room 22.8 C.
11:48	31.42	
11:49	31.49	
11:50	31.53	At 11:50 anesthetic phalanges put in water at 42.8 C.
11:51	31.55	
11:52	31.59	Room 22.6 C.
11:53	31.62	
11:54	31.675	Room 22.6 C.
11:55	31.73	Room 22.5 C.
11:56	31.77	
11:57	31.81	Room 22.5 C.
11:58	31.8/	
11:59	31.915	
12:00	31.965	At 12:00, 7 phalanges of left hand put in water at 42 C.
12:01	31.995	
12:02	32.02	Room 22.7 C.
12:03	32.06	Room 22.8 C.
12:04	32.10	
12:05	32.155	
12:06	32.20	
12:07	32.26	Room 23 C.
12:08	32.25	
12:09	32.32	Room 23.1 C.
12:10	32.35	
12:11	32.39	
12:12	32.43	Room 23.1 C. At 12:12 the 7 phalanges put in water at 8.2 C.
12:13	32.46	
12:14	32.48	
12:15	32.51	Room 23.2 C.
12:16	32.535	
12:17	32.56	Room 23.35 C.
12:18	32.585	
12:19	32.605	
12:20	32.63	Room 23.3 C.
12:21	32.655	At 12:21 whole left hand put in water at 43 C.
12:22	32.68	
12:23	32.705	Room 23.4 C.
12:24	32.74	
12:25	32.78	
12:26	32.82	
12:27	32.86	Room 23.3 C.
12:28	32.90	
12:29	32.945	Room 23.2 C.
12:30	33.02	Hand out of calorimeter at 12:30.
12:44	32.86	
.....	.....	Cooling of calorimeter R 0.16 degrees in 14 minutes.
.....	.....	Cooling of control calorimeter (without hand) from 30.53 to 29.76 degrees, or 0.77 degrees in 71 minutes.
.....	.....	Rectal temperature 37 C.
.....	.....	Vol. of right hand 431 c.c.

In the experiment of December 19 the flow for ten minutes before the vasomotor reflex was tested was 10.63 grams per 100 c.c. per minute for

the right hand and 10.23 grams for the left. For the first two minutes of immersion of the anesthetic phalanges of the left hand in cold water the flow in the right hand sank to 5.21 grams, rising again to 9.15 grams per 100 c.c. per minute for the remaining eight minutes during which the anesthetic phalanges continued in the cold water. On transferring the anesthetic phalanges to warm water the flow in the right hand diminished for the first four minutes to 7.80 grams per 100 c.c. per minute, to increase again to 9.45 grams for the remaining seven minutes of the period of immersion. When the whole left hand was immersed in

TABLE 4.—SUMMARY OF BLOOD-

Date.	Temp. C. of Calorimeter				Vol. of Hands, c.c.		Heat given off (small cals.)		
	Room.	R.	L.	Art. Blood.	R.	L.	R.	L.	In mins.
Oct. 15	22.6	31.32	31.35	36.65	447	436	2537	2273	16
	22.8	31.61	.....	.....	...	...	155	....	2
	22.9	31.72	.....	.....	...	...	1053	....	7
	23.0	31.87	.....	.....	...	...	431	....	3
	23.1	32.04	.....	.....	...	...	1157	....	5
	32.2	32.23	.....	.....	...	...	638	....	4
	23.2	32.39	.....	.....	...	...	915	....	4
	23.3	32.55	.....	.....	...	...	956	....	8
Dec. 19	23.3	31.17	31.17	36.55	431	407	2219	2018	10
	23.3	31.46	.....	.....	...	...	206	....	2
	23.3	31.64	.....	.....	...	...	1394	....	8
	23.3	31.87	.....	.....	...	...	567	....	4
	23.35	32.06	.....	.....	...	...	1153	....	7
	23.3	32.25	.....	.....	...	...	464	....	3
	23.3	32.50	.....	.....	...	...	1669	....	8
	23.2	32.81	.....	.....	...	...	1032	....	9
	23.25	33.01	.....	.....	...	...	1032	....	8
Dec. 21	22.9	30.82	.....	36.50	431	...	2012	....	9
	22.9	31.10	.....	.....	...	...	242	....	2
	22.9	31.33	.....	.....	...	...	1684	....	8
	22.6	31.58	.....	.....	...	...	416	....	3
	22.5	31.79	.....	.....	...	...	1448	....	7
	22.7	31.99	.....	.....	...	...	263	....	2
	22.95	32.23	.....	.....	...	...	1782	....	10
	23.25	32.54	.....	.....	...	...	1110	....	9
	23.35	32.70	.....	.....	...	...	440	....	3
	23.25	32.98	.....	.....	...	...	1160	....	6

the warm water the flow in the right hand for the first three minutes was 9.27 grams, which increased to 13.27 grams per 100 c.c. per minute for the remaining eight minutes of the period. The whole left hand was then put into cold water and the flow in the right sank to 7.90 grams per 100 c.c. per minute during the nine minutes of immersion, to rise again to 9.39 grams (over a period of eight minutes) when the left hand was dried and wrapped up.

In both of the above experiments the two hands were originally in the calorimeters. In order to test the effect of the immersion on the anesthetic phalanges alone, the left hand had to be taken out and dried.

Although the drying was carefully done, it might be objected that the effect on the flow in the right hand following the first immersion of the anesthetic phalanges was really due to stimulation of the temperature nerves in the normal portions of the still moist left hand. Of course, this possibility could only apply to the first immersion of the anesthetic phalanges and not to succeeding immersions. Yet it was considered desirable to eliminate it and this was done in the experiment of Dec. 21, 1912, in which only the right hand was put into a calorimeter, the left being kept dry until the moment for immersion of the anesthetic phal-

FLOW OBSERVATIONS ON O. C. W.

Flow in Hands per min.		Flow per 100 c.c. per min.		
R.	L.	R.	L.	Notes.
33.05	29.78	7.39	6.83	Before vasomotor reflex tests.
17.08	.....	3.82	.....	Anesthetic phals. in cold water (first 2 mins.).
33.90	.....	7.58	.....	Anesthetic phals. in cold water (next 7 mins.).
33.39	.....	7.24	.....	Anesthetic phals. in warm water (first 3 mins.).
55.77	.....	12.47	.....	Anesthetic phals. in warm water (next 5 mins.).
40.09	.....	8.96	.....	Whole left hand in warm water (first 4 mins.).
59.66	.....	13.34	.....	Whole left hand in warm water (next 4 mins.).
32.38	.....	7.24	.....	Whole left hand in cold water
45.82	41.67	10.63	10.23	Before vasomotor reflex tested.
22.48	.....	5.21	.....	Anesthetic phals. in cold water (first 2 mins.).
39.43	.....	9.15	.....	Anesthetic phals. in cold water (next 8 mins.).
33.65	.....	7.80	.....	Anesthetic phals. in warm water (first 4 mins.).
40.76	.....	9.45	.....	Anesthetic phals in warm water (next 7 mins.).
39.96	.....	9.27	.....	Whole left hand in warm water (first 3 mins.).
57.23	.....	13.27	.....	Whole left hand in warm water (next 8 mins.).
34.06	.....	7.90	.....	Whole left hand in warm water (first 3 mins.).
40.49	.....	9.39	.....	Whole left hand dried and wrapped up.
43.73	.....	10.14	.....	Before vasomotor tests.
24.89	.....	5.77	.....	Anesthetic phals. in cold water (first 2 mins.).
45.26	.....	10.50	.....	Anesthetic phals. in cold water (next 8 mins.).
31.31	.....	7.28	.....	Anesthetic phals. in warm water (first 3 mins.).
48.79	.....	11.32	.....	Anesthetic phals. in warm water (next 7 mins.).
32.39	.....	7.51	.....	7 phals. left hand in warm water (1st 2 mins.).
46.37	.....	10.75	.....	7 phals. left hand in warm water (next 10 min.).
34.60	.....	8.02	.....	7 phals. of left hand in cold water.
43.27	.....	10.04	.....	Whole left hand in cold water.
61.02	.....	14.15	.....	Whole left hand in warm water (next 6 mins.).

anges. As in the previous experiment, a sheet of thick cork with a hole through which the anesthetic phalanges passed prevented any contact of the rest of the hand with the cold or warm water or the container.

It will be seen that the results are precisely the same as in the other experiments. For nine minutes before testing the vasomotor reflex the flow in the right hand comes out 10.14 grams per 100 c.c. per minute. For the first two minutes of immersion of the anesthetic phalanges of the left hand in cold water, the flow in the right sinks to 5.77 grams, to increase to 10.50 grams per 100 c.c. per minute for the remaining eight

minutes of immersion. When the anesthetic phalanges were now immersed in warm water (the change from the cold to the warm water was made instantaneously without taking the phalanges out of the cork) the flow diminished for the first three minutes to 7.28 grams, to increase to 11.22 grams per 100 c.c. per minute for the remaining seven minutes of the period of immersion. Immersion in warm water of seven phalanges (second and third of index, middle and ring, and third of little finger) of the left hand, including the anesthetic phalanges, caused now a diminution of the flow in the right hand for the first two minutes to 7.51 grams per 100 c.c. per minute. For the remainder of the period during which these phalanges continued in the warm water (ten minutes) the flow rose to 10.75 grams per 100 c.c. per minute. For nine minutes during the immersion of these phalanges in cold water the flow in the right hand declined to 8.02 grams, a more persistent diminution than was caused by immersion of the anesthetic phalanges alone. When the whole left hand was subsequently put into warm water, an increase ensued in the flow in the right hand to 10.04 grams per 100 c.c. per minute for the first three minutes and 14.15 grams for the remaining six minutes of immersion, the greatest flow witnessed throughout the observation on this case.

In all three experiments, then, a change is produced in the blood-flow in the right hand when a portion of the left hand, totally insensitive to warmth or cold (as well as to other forms of sensation), is immersed in warm or cold water. Although the effect is smaller and more transient than that produced by immersion of the sensitive portions of the left hand, it is too definite to be attributed to accidental changes in the circulation.

The question has already been raised in discussing a similar reaction elicited from parts totally devoid of temperature sensibility in a pathological case,[1] whether afferent impulses capable of affecting vasomotor centers can be conducted by the nerves of warmth and cold sensation when they are unable to conduct impulses, at least in sufficient intensity, which give rise to temperature sensations, or whether the reactions are elicited through nerves, for example, those supplying the deeper structures, which can be excited by abrupt variations of temperature, although no result is produced in consciousness, and which can act as the afferent link in the vasomotor reflex arc. The possibility also presented itself that the blood in the anesthetic phalanges was sufficiently cooled or heated during the immersion to cause excitation of nerve endings in parts above the level of the anesthesia. In regard to this last possibility it must be remarked that since no sensation of heat or cold was experienced in such neighboring parts, the suggestion is really included in the ques-

tion as already stated. In the hope of throwing some light on this question plethysmographic observations were made with a view of determining the latent period of the contralateral reflex elicited from the anesthetic phalanges. A finger plethysmograph was adjusted on the opposite hand. The moment of immersion of the anesthetic phalanges was written above the plethysmogram by an electromagnetic signal. It was foreseen that unless this latent period should turn out to be markedly lengthened no deductions could be drawn as to whether conduction of heat to or from a deeper layer than usual or convection of heat in the blood to neighboring parts was essential. For we neither know how rapidly heat would be conducted through a finger with the circulation going on, nor how great a change of temperature would be necessary to excite nerves which gave no sign by a sensation of temperature when the threshold had been reached. As a matter of fact, the latent period turned out to be quite small and not measurably greater than when the reaction was elicited from normal skin (Fig. 1). The description of the figure sufficiently elucidates the results. It is, however, worthy of special remark that when the second and third phalanges of the index finger of the left hand were enclosed in the plethysmograph no vasomotor reflex could be elicited from the right hand, even when the whole of that hand was immersed in warm or cold water. The meaning of this can only be that the efferent vasomotor fibers going to the index finger or their endings have not yet regenerated to the point at which they can conduct effective impulses. It is entirely in accordance with this that the spontaneous variations in the finger volume not connected with the respiratory movements and with a period covering several respirations which sometimes appear on the trace of the right middle finger, are absent from the trace of the left index finger. If these non-respiratory waves represent more or less rhythmical variations in vasomotor tone they must be absent from a part whose efferent vasomotor fibers are eliminated. We thus arrive at the conclusion that at a time when the efferent vasomotor fibers of a given part have not regenerated, afferent impulses from the same part elicited by heat or cold and producing no effect in consciousness can cause vasomotor reflexes. It must be remembered that the efferent vasomotor fibers in question are autonomic fibers whose cells of origin are in sympathetic ganglia, whereas the afferent fibers are cerebrospinal, their cells of origin being in the posterior root ganglia. In connection with the vasomotor paralysis of the anesthetic phalanges, the extremely rapid and persistent transudation of liquid into the blister on the terminal phalanx of the index finger is a matter of interest. The normal healing of the region, for it was not in the least delayed nor did any complication what-

ever appear, does not tally with the idea that any essential trophic influence had been removed by the injury to the cutaneous nerves.[3]

3. Additional note.—March 19, 1913. Peripheral reference of cold (to the tip of the index finger) has now been observed for the past ten days when a cold object touches a definite part of the scar in the forearm. It is elicited by the point (2 mm. in diameter) of a cylinder filled with ice but more intensely with a larger surface. The local response is inferior in intensity to the referred sensation. No peripheral reference of heat is obtained (confirmatory of Trotter and Davies[2]). No peripheral reference of cold as yet from any other part of the skin. The second and third phalanges of the middle and index fingers still give no response to hot or cold cylinders. But prolonged immersion in water at 43 C. (as in the blood-flow measurements) now causes the slow development of "something like a warm sensation," and in water at 8 C. "tingling as if from cold." Light stroking, contact with a blunt point, and pressure are now appreciated over the whole hand. The index finger is now hypersensitive to stroking (except the dorsum of the third phalanx) and appreciates pain on very strong pressure, as on biting the finger. Blood-flow observations in the hands show essentially the same features as at the previous examinations.

A METHOD FOR THE QUANTITATIVE DETERMINATION OF PEPSIN BY USING A COLLOIDAL SUSPENSION OF EGG ALBUMIN *

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INTRODUCTORY NOTE

The experimental work in this paper was done during October, November and December, 1909, and January, 1910. A report of the work was made before the St. Louis Medical Science Club in February, 1910. The work was repeated during the year 1911 and read before the St. Louis Society of Internal Medicine in May, 1911. About this time our attention was called to the work of Hata, which was unknown to us. This work is practically identical with our method except in some points of technic. Hata's paper was published in November, 1909. After reading this paper we decided not to publish our results. As Hata's work has received practically no attention, it seemed important to us that this work should be known. It is a valuable method for the quantitative determination of pepsin. We submit this paper as a confirmation of Hata's work. We think our method of procedure easier and better adapted for clinical work than Hata's.

Many methods have been worked out for the quantitative determination of pepsin. Among these, Hammerschlag's method may be mentioned. It is open to the objection that the method of estimating the amount of undigested albumin is determined by Esbach's method, which is inaccurate. Mett's ingenious method has not proved accurate. This method takes ten to twelve hours to complete the determination. Nierenstein and Schiff's modification of Mett's method takes twenty-four hours for its completion. According to Sahli, Volhard's method is better than Mett's method for showing digestion in gastric contents containing but little pepsin. This method is too complicated for ordinary use.

Grützener's carmin method is simple but requires the use of a colorimeter. It also has the objection that its solutions are not stable. The Jacoby and Solms ricin method is valuable, but unfortunately requires an impure form of ricin which is not easily obtained. Their ricin solution gradually deteriorates so that gastric contents tested with old solutions show too high a pepsin content. Fuld and Levison's method requires a

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vegetable protein, edestin, which is difficult to prepare or obtain. This solution also deteriorates on standing. The Gross method is simple in its technic and the material, casein, is easily obtained.

Schorer's refractometric method seems valuable but it is not adapted for general use. Illoway's method is simple but takes too long to complete the determination. Several other methods such as Meunier's, Bettman and Schroder's, Spriggs' and Lieberman's have been reported but have not been extensively used.

In studying these different methods to determine which was most applicable to a problem we had in hand, we decided on the Jacoby-Solms method. We were unable to obtain the impure ricin used by them without importing. While waiting for this we studied their method carefully. It occurred to us that the probable explanation of the Jacoby-Solms method was due to a protein in the impure ricin which was made colloidal by their procedure, because their solution becomes opalescent when ready for use. On investigating the Fuld and Levison method, or edestin method, we found their solution to be opalescent and therefore, in all probability, edestin is a colloidal condition. With these facts in mind it occurred to us that the colloidal egg albumin solution of Hardy might be used for a quantitative determination of pepsin by the dilution or limit method.

Hardy has shown that egg albumin diluted with distilled water in the proportion of one part egg albumin to nine parts of water, filtered and heated, becomes opalescent. By dialysis and the use of the electric current on this solution in faintly acid or alkaline reaction, he has proved its colloidal nature. This colloidal egg albumin solution is used by us in our method of determining the quantity of pepsin in gastric contents.

METHOD OF MAKING THE COLLOIDAL ALBUMIN SOLUTION

Our method of making this solution is similar to Hardy's. The white of egg is separated from the yolk and is thoroughly beaten, or, better, vigorously shaken in a flask. It is allowed to stand after shaking until the air bubbles disappear. A measured quantity is diluted nine times with water and filtered through ordinary qualitative filter paper. It comes through the filter paper clear and transparent. The solution is acidified slightly by adding two or three drops of an 0.8 per cent. solution of hydrochloric acid to 100 c.c. of the albumin solution. With the albumin of some eggs it is unnecessary to acidify as the albumin becomes opalescent on heating. In other eggs the albumin solution remains clear when heated. This is especially so if the eggs are old. In our method of making the albumin solution we always acidify, as the results are then constant. Hardy does not acidify and, as a result, the solution does not always become opalescent on heating. Hardy's instructions as to the manner of heating are rather indefinite, so that a certain number of failures result even if the albumin solution is acidified. The heating should be done slowly and the temperature should not be raised higher than 60 or 65 C. If the solution is heated too rapidly the albumin solution remains clear and transparent. By heating slowly the solution can be made in

large quantities instead of using small test-tubes as Hardy suggests. We heat the solution in a large test-tube of 100 c.c. capacity or in an Erlenmeyer flask over a naked flame. Made in this way, we invariably obtain an opalescent solution which has all the colloidal properties of Hardy's solution.

METHOD OF MAKING THE COLLOIDAL ALBUMIN SOLUTION READY FOR DIGESTION EXPERIMENTS

To every 100 c.c. of albumin solution 50 c.c. of an 0.8 per cent. hydrochloric acid are added. When a few cubic centimeters of this acid are first added a precipitate may form which will clear as the remainder of the acid is added. The resulting solution is a clear opalescent solution, but somewhat lighter in color than the original, as it has been diluted one-third with the acid. We may, for convenience, call this a stock solution of albumin.

METHOD OF ESTIMATING THE PEPSIN

All the gastric contents are those of students. The gastric contents were removed at 8 a. m., one hour after a Boas-Ewald test breakfast had been given. The gastric contents were filtered and the pepsin tests made at once. The next step is to make four preliminary dilutions of the filtered gastric content.

Tube 1, 2 c.c. gastric content, 23 c.c. distilled water make a dilution 1 to 12.5.
Tube 2, 2 c.c. of tube 1. 2 c.c. distilled water make a dilution 1 to 25
Tube 3, 2 c.c. of tube 1. 4 c.c. distilled water make a dilution 1 to 37.5
Tube 4, 2 c.c. of tube 1. 6 c.c. distilled water make a dilution 1 to 50

Into four small test tubes 3 c.c. of the stock colloidal albumin are placed. Into each of these tubes, 1 c.c. of the preliminary dilution is placed, commencing with the weakest solution first in order to avoid the more rapid action of the stronger solutions as these others are added. The time error is so small by this method that it is ignored, as it only takes a few seconds to mix the solutions in the four tubes. The tubes were shaken to insure thorough mixing, placed in a water-bath registering 38.5 to 40 C. and the time of placing them in the water-bath is noted. If the method of diluting is placed in table form it may appear clearer.

PRELIMINARY DILUTIONS OF GASTRIC JUICE

1. Dilution 1 to 12.5
2. Dilution 1 to 25.
3. Dilution 1 to 37.5
4. Dilution 1 to 50.

FINAL DILUTIONS IN THE COLLOIDAL ALBUMIN SOLUTION

3 c.c. of acidified albumin solution 1 c.c. tube 1 makes a dilution 1 to 50
3 c.c. of acidified albumin solution 1 c.c. tube 2 makes a dilution 1 to 100
3 c.c. of acidified albumin solution 1 c.c. tube 3 makes a dilution 1 to 150
3 c.c. of acidified albumin solution 1 c.c. tube 4 makes a dilution 1 to 200

By consulting the accompanying table it is seen that the resulting solutions in the digesting tubes must be 1 to 50, etc. For instance, 1 c.c. of Tube 1, dilution 1 to 12.5, diluted with 3 c.c. of stock albumin solution must be 1 to 50, etc. Furthermore, by this method of procedure the percentage of acid in the digesting tubes is 0.2 per cent. For instance, 1 c.c. of 0.8 per cent. HCl in 3 c.c. of solution makes a 0.2 per cent. solution of hydrochloric acid. The amount of acid in the 1 c.c. of each dilution of the gastric content is ignored, as we have found such small quantities without appreciable influence on the time of digestion.

No	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38				
Total Acidity	30	70	55	75	66	60	85	80	82	70	70	48	78	95	85	67	77	85	65	65	60	65	50	74	76	66	90	50	45	60	95	60	70	60	63	85	75	87				
G.C Dilution	Time required for clearing (minutes)																																						I Average	Proportion	II Average less 1/50 dilution	Proportion
1/50	24	17	19	13	33	14	21	11	15	12	23	21	12	10	8	19	25	20	13	21	14	17	23	15	14	20	18	20	13	20	14	13	25	12	17	21	14	19	17.3	1	16.2	1
1/100	45	22	29	29	40	26	31	17	28	30	29	35	19	15	13	30	38	27	22	29	25	33	40	23	23	25	30	40	19	47	36	30	39	16	26	38	20	48	29	1.67	27.5	1.69
1/150	40	27	42	32	43	31	42	21	45	40	24	47	30	25	31	42	50	41	34	41	36	40	60	34	31	32	36	75	38	60	55	48	55	26	47	68	37	55	42.2	2.45	38.7	2.38
1/200	70	32	47	41	80	35	50	24	52	60	45	60	35	32	37	55	65	53	50	54	51	55	75	45	47	45	57	90	50	75	65	60	65	32	65	77	36	70	53.5	3.08	49.7	3.06

Table Showing Total Acidity, Dilution and Time Required for Clearing in the Digestion of a Colloidal Suspension of Egg Albumin

After the tubes have been placed in the water bath, the tube with dilution 1 to 50 is removed at short intervals and examined to determine whether digestion is complete in that tube. Each tube is taken in the order of its dilution and the time of its digestion noted. The end-point of the digestion is when the opalescence has disappeared and the solutions are practically clear. There is always a faint, cloudy appearance after the opalescence disappears. At first this end-point may seem uncertain; but after a few trials one determines this easily. In examining the tubes they must not be placed in direct sunlight or strong light. We read all our tubes at the north window of the laboratory where there is a clear, diffused, reflected light.

The results in this table are consecutive tests made on thirty-eight gastric contents of students. These are considered normal gastric contents as none of them differ much from the so-called normal standard of quantity of gastric contents and total acidity of a Boas-Ewald test breakfast.

It is seen that on the whole, the results are as uniform as we could expect. There is some variation in the time of digestion but not more than in the total acidity. The time of digestion is not proportional to the dilution as the more dilute solutions of the gastric contents digest relatively quicker than the more concentrated.

If we consider the time it takes a dilution of 1 to 50 to digest as one, we find the ratio 1,-1.67,-2.4,-3 instead of 1,-2,-3,-4, the ratio by dilution. The column of averages, No. 1, is made by averaging the time digesting all the 38 gastric contents. Column No. 2 is made by averaging all except 1, 5, 23, 28 and 36, which digested so much slower than the others as to be somewhat out of proportion to the others. The ratio here is 1,-1.68, 2.4,-2.98, which is practically the same as that of all the contents.

By this method of procedure, supposedly normal gastric contents in a dilution of 1 to 100 will clear colloidal egg albumin approximately in one-half hour. In gastric analysis we consider a normal total acidity between 40 and 70. In a determination of pepsin by this method we might consider the pepsin as normal when digestion is finished in a dilution of 1 to 100 in twenty-five to thirty-five minutes. If in this dilution, digestion is completed more rapidly than thirty minutes, we know there is plenty of pepsin. The only question is how far above thirty minutes we may make the limit and still be within so-called normal limits. It seems to us that a digestion in twenty-five to thirty-five minutes should still be considered normal, as the general average for this dilution is twenty-nine minutes.

In another set of experiments on the gastric contents of thirty-four different students, by a different method of diluting, we obtained the following general average:

Dilution	Average, Minutes	Dilution	Average, Minutes
1-8	6.0	1-122	38.0
1-20	9.5	1-140	44.0
1-40	14.0	1-160	50.5
1-80	23.5	1-200	57.0
1-100	30.0		

We see here the general averages approach those of the other set of experiments.

Instead of using the time of digesting as a standard we might establish an arbitrary standard. If we consider the digesting power of a dilution of 1 to 100 in thirty minutes as 100, we would have a standard for comparison. If a pure gastric content digested the solution in a dilution of 1 to 100 in forty minutes, the pepsin power would be less as the time of digestion was longer. In units this would be 67, as the digestion was 33 per cent. slower. Or if the digestion in the dilution was completed in twenty minutes, the pepsin units would be 133, etc. The normal limits would vary between 85-116; we take the limit as varying between twenty-five and thirty-five minutes.

In the routine examination of gastric contents for the quantitative determination of pepsin, all that is necessary at first would be the making a dilution of 1 to 100 and note the time of the digestion. If this took place between twenty-five and thirty-five minutes we could consider the digestion normal. If it took much longer or did not clear up at all, stronger solution should be used. Let us say a dilution of 1 to 10, 1 to 25. If these cleared in twenty-five to thirty-five minutes the digestion power in units would be 1/10, 1/25 of 100. Any other dilution that the worker might desire to use could easily be made. Dilutions might be made as follows:

3 c.c. acidified albumin 1 c.c. filtered gastric content makes dilution 1-4
3 c.c. acidified albumin 1 c.c. of 1 to 25 dilution makes dilution 1-10
3 c.c. acidified albumin 1 c.c. of 1 to 6.25 dilution makes dilution 1-25

In making up small quantities of the albumin solution for use at different times, it occurred to us that the albumin of different eggs might vary in concentration and thus the time of digestion might also vary, when the solution of different eggs was used. We tried a 2 per cent. solution of pepsin on different eggs and found no marked variations. We also tried a gastric content in different dilutions on two dozen different eggs and found the results practically constant.

There is another question which is of importance; that is, whether the acidified albumin solution is stable. These solutions will keep about ten days or two weeks, but at the end of that time the albumin begins to precipitate and, as a result, the time of digestion is shortened. We also found that the end-point in the old solutions is not so sharp as in the fresh solutions.

The acidified albumin solution with chloroform added in the proportion of one part chloroform to 1,000 albumin solution, keeps from two to three weeks. At the end of three weeks there may be no precipitate of albumin, yet the end-point is not sharp and the resulting time of digestion is somewhat inaccurate.

The time of digestion is not proportional to the quantity of pepsin as measured by the dilution. As the solution of gastric contents becomes more dilute the time of digestion gradually lessens. This suggests the possibility that in the dilution methods such as we have used, we do not obtain the same result we would obtain if the digestion were carried on in undiluted gastric contents. By diluting we may lessen certain inhibitory factors which operate in concentrated gastric contents but not in dilute solutions. However, the results obtained by this method approximate closely the digestive power of a given gastric content. Any marked pathological change in the digestive power of a given gastric content will surely be found by this method, as we have shown conclusively in pathologic cases.

The concentration of hydrochloric acid for the most rapid digestion with this albumin solution is 0.1 per cent. The time of digestion is proportional to the concentration of the albumin used.

The points in favor of this method are:

1. We have a material which is easily obtained.
2. The colloidal albumin solution is easily made.
3. The technic is as simple as any dilution method can be.
4. The time of making a complete determination is under one hour.
5. The results are constant.

Objections to this method:

1. The solution cannot be kept and used indefinitely, as it decomposes.
2. It has the objection that dilution methods do not give the actual digestion as found in concentrated gastric contents.
3. The end-point may seem indefinite to those who use this method for the first time; but experience soon enables one to read and obtain constant results.

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HEART SIZE AND HEART FUNCTION IN CHILDREN SHOWING ORTHOSTATIC ALBUMINURIA: AN ORTHODIAGRAPHIC STUDY *

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The close relationship of orthostatic albuminuria to the cardiovascular system has frequently been emphasized, yet in a consideration of the literature one is struck by the diversity of opinions and the contrary findings of various authors. Having at our disposal the material of a large pediatric clinic and noting how frequently cases of orthostatic albuminuria presented themselves for treatment, we determined to study the hearts and blood-pressures in a number of these patients in order to see which of the previous findings we could corroborate, and also whether in the course of our work we could throw some light on the pathogenesis of these symptoms.

The present paper will deal only with our results in the examination of the heart, and we leave a consideration of the blood-pressures to a future communication.

Ever since Edel[1] called attention to the cardiovascular factor as an important one in the etiology of orthostatic albuminuria, many observations have been made, both on the heart and the vessels, in an attempt to clear up this obscure subject. Although various investigations have not as yet been able to solve the problem, nevertheless in their course a considerable amount of interesting data has been brought forward. At first there was a tendency to explain the albuminuria purely as the result of a cardiovascular abnormality, but it soon became clear that urine of a similar character was excreted by children in whom no physical abnormalities could be detected. On the other hand, it had been noted that a large number of children who showed this urinary anomaly also presented cardiovascular peculiarities. These symptoms appeared to be more or less characteristic, and led Langstein[2] to classify his cases of orthostatic albuminuria in three groups: 1. Children who have grown rapidly, who complain of fatigue, palpitation and headache, look pale, but whose hemoglobin is normal. This type usually occurring in girls of 12 to 14 years, Langstein terms the angiospastic type. 2. Children

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* From the Dispensing and X-Ray Departments of Mt. Sinai Hospital.
1. Edel: München. med. Wchnschr., 1901, Nos. 46 and 47.
2. Langstein: Die Albuminurien älterer Kinder, Monograph, Leipzig, 1907.

who flush easily, who show marked vascular irritability, whose complaints are chiefly congestive headaches, vomiting attacks and urticaria. These cases he groups as the erethic type. 3. Children whose physical examination shows no abnormality and who have no complaints. In such cases the albuminuria is incidentally found in a routine examination.

It appears, therefore, both from previous observations and from the cases we are about to describe, that when subjective symptoms do occur in orthostatic albuminuria they are chiefly those referable to the cardiovascular system, viz., dyspnea on exertion, palpitation, precordial pain, headache, fainting, hypersusceptibility to cold. These symptoms, coming on as a rule in children between the ages of 10 and 14, have become intimately associated with the symptomatology of puberty. This connection has long been noted, and has led to numerous hypotheses in which a disproportion between the growth of the various organs and the work they are called on to perform at this period of rapid bodily development has been assumed as the basis of these symptoms. An analogy is seen between the albuminuria, which is supposedly due to an insufficiency of the kidney, unable in its growth to keep pace with the rest of the body, and the cardiac symptoms which are an expression of a similar developmental backwardness of the heart.

The material on which this report is based comprises thirty-six dispensary cases, who during the previous fourteen months applied for treatment for a variety of complaints. These complaints, coupled with the more or less characteristic appearance of the children, led us to suspect albuminuria. In each case albumin was shown to be present in the urine by the addition of dilute acetic acid and the application of heat. The albuminuria was then proved to be of the orthostatic variety by the examination of several specimens of the early morning urine, which was found to be albumin free. In a few of the cases albumin only appeared in the urine after the child was placed in the lordotic position by kneeling as described by Jehle.[3] In all the cases the albumin disappeared on the assumption of the horizontal position. In none of the cases were casts found, though centrifuged specimens of the urine were frequently examined, some of them over a period of a year. These cases were subjected to a functional heart examination in the following manner:

A complete physical examination of each child was made in such a manner that the element of fear or nervousness on the part of the child could be excluded as much as possible. Then on another day the heart size was determined by orthodiagraphy in the sitting posture and the pulse-rate taken. The child was next made to run up and down four flights of stairs rapidly and was then immediately orthodiagraphed a second time and the pulse again counted. The fluoroscopic examination was always done at the same time of the day, sufficiently removed from meal-time to obviate sources of error. The orthodiagraph was in every case made by the same one of us and the physical examination by the other so that the personal element might be eliminated.

3. Jehle: Die Lordotische Albuminurie, Leipzig and Wien, 1909.

EXAMINATION OF THE HEART AT REST

In Table 1 will be found the results of the orthodiagraphic examination of these thirty-six children while at rest. In the fifth column are given the average figures of heart size for children of corresponding heights as determined by Veith.[4] A comparison of these figures shows seven of the hearts to be larger than normal. Of these seven cases, six show an increase over the normal of but 1 to 3 mm., differences within the limits of error. This leaves one case (Case 18) in which the heart is distinctly enlarged. Of the remaining twenty-nine cases, twenty-two show values lower than the normal. It is remarkable that the majority of these figures differ from the normal by relatively large amounts — from 1 to 4 cm. In this chart we have included all our cases of orthostatic albuminuria irrespective of the presence or absence of cardiac symptoms. Included in these, however, are fifteen children who either complained of subjective symptoms or presented signs of cardiac abnormality on physical examination. It is, therefore, of interest to determine whether these fifteen can be differentiated from the others in respect to heart size. This is of especial importance in view of the effort which has been made by investigators for some years to find in an alteration in heart size and function an explanation of these very symptoms.

French and German clinicians have advanced various theories to explain these symptoms.[5] As has been mentioned above, it appeared to most observers that since many of these cases occurred at or immediately before puberty, owing to a lack of correspondence of growth between the heart and the body, a relative insufficiency of the former became manifest, accentuated by the excessive psychical and physical demands of the growing body. This weakness showed itself, especially in children, who by heredity or environment, were handicapped by poor physical development. The ensuing malnutrition also expressed itself in poorly developed hearts, with the results that the demands of even every-day life were the cause of subjective and objective signs of heart insufficiency, such as in normal individuals would be manifest only after considerable exertion. To quote Martius[6]: "Heart weakness without expressly discoverable cause, brought about by the ordinary demands of life, incidental to the school age." The same idea has been aptly expressed by Fairbanks,[7] who, in speaking of the "Essential Insufficiency of the Heart in Childhood," says: "One reason why the aggregate of demands on the heart may sometimes exceed its power to respond lies in the fact that the general bodily development is neither synchronous nor symmetrical."

4. Veith: Pahrb. f. Kinderh., 1908, lxviii, 205.
5. Lommel: Krankheiten des Jünglingsalters, Ergeb. d. inn. Med. u. Kinderh., 1910, vi.
6. Martius: Kongress f. inn. Med., 1899, p. 41.
7. Fairbanks: Jour. Am. Med. Assn., 1907, xlix, 1976.

This clinical picture, to which Germain Sée[8] first called attention in 1889, and to which he gave the name *"Hypertrophie et dilatation de la croissance,"* was further developed and more completely described by Martius.[9] In the examination of a large number of institution children this observer was impressed by the existence of a distinct group presenting the following typical appearance:

> The children are weak, pale, lose their appetite, complain of headache. . . . Examination reveals besides slight enlargement of the cervical nodes, moderate anemia, sometimes but not always orthostatic albuminuria, the absolutely characteristic heart finding-dilatative weakness.

According to Martius, in this condition the physical signs are characteristic. The apex-beat of the heart is displaced beyond the nipple, sometimes out as far as the anterior axillary line; it is heaving in character; the pulse shows distinct diminution in tension and has a tendency after exercise to increase in rate out of all proportion to the amount of the exertion and at the same time to become very poor in quality. This condition Martius considers frequent among the poorer classes.

While during the past decade orthostatic albuminuria was arousing considerable interest[10] and the children suffering from it were subjected to careful study, it became apparent that a great number of them belonged to the above group described by Martius, the albuminurics showing cardiac signs and symptoms identical with those classed as dilatative weakness. Thus in ninety cases of orthostatic albuminuria Lommel[11] found thirty-eight with cardiac abnormalities, thirteen with apparent left ventricle hypertrophy, eleven with markedly exaggerated apex-beat and nine with systolic murmurs. Schaps[12] in the same way notes a big percentage of enlarged hearts with subjective symptoms. The idea was, therefore, generally accepted that many orthostatic albumiurics had cardiac enlargement. It must be remembered, however, that these observations were made before the introduction of the more precise methods of examination afforded by the *x*-rays, and it is therefore of considerable interest to find that when a few similar cases were subjected to fluoroscopic examination no enlargement of the heart was found. Fischl[13] who skiagraphed these hearts found them normal, while Langstein and Reyher,[2] using the orthodiagraph, found to their surpise that in eight cases so examined the hearts were smaller than usual. This

8. Germain Sée: Traite des maladies du coeur. 1889.
9. Martius: *Loc. cit.* Note 6, and Gedenkschrift für von Leuthold, 1906.
10. For a review of the latest literature on this subject see Bass: A Summary of the Recent Literature on Orthostatic Albuminuria. Am. Jour. Dis. Child., 1912, iv, 246.
11. Lommel: Arch. f. klin. Med., 1903, No. 78, p. 540.
12. Schaps: Arch. f. Kinderh., 1903, No. 35.
13. Fischl: Arch. f. Kinderh., 1909, lii.

TABLE 1.—HEART SIZE DURING REST IN THIRTY-SIX CASES OF ORTHOSTATIC ALBUMINURIA; TWENTY-SIX GIRLS AND TEN BOYS*

Case No.	Age	Height, cm.	Heart Size, Transverse Diameter, cm.	Normal Heart Size (Veith), cm.	Difference, cm.		Symptoms and Physical Signs
1	....	9	115	8.2	8.8	— .6	Palpitation, dyspnea.
2	....	10	129	8.6	9.4	— .8	Palpitation, dyspnea.
3	....	11	130	8.4	9.4	—1.0	Palpitation, dyspnea, booming first sound.
4	....	8	132	8.7	9.87	—1.1	Palpitation, dyspnea, booming first sound, pulmonic second accentuated.
5	....	14	136	8.2	9.87	—1.6	Palpitation, dyspnea, first sound impure, pulmonic second accentuated.
6	....	14	140	9.4	9.87	— .4	Palpitation, dyspnea, booming first sound.
7	....	13	151	9.1	11.3	—2.2	Palpitation, dyspnea, overaction.
8	....	10	131	9.1	9.87	— .7	Palpitation, dyspnea, apex one finger outside nipple, overaction.
9	....	10½	126	9.6	9.4	+ .2	Palpitation, dyspnea, left border one finger outside nipple.
10	....	8	121	8.2	9.4	—1.2	Palpitation, dyspnea, apical systolic murmur, pulmonic second accentuated.
11	....	11	133	8.7	9.87	—1.1	Palpitation, dyspnea, apical systolic murmur.
12	....	12	137	7.8	9.87	—2.	Palpitation, dyspnea, apical systolic murmer, overaction.
13	....	7	115	9.1	8.8	+ .3	Palpitation, dyspnea, heaving apical impulse, booming first sound.
14	....	14	150	10.	10.39	— .3	Palpitation, dyspnea, apex outside nipple, heaving impulse, overaction, accentuated pulmonic second.
15	....	12	140	9.3	9.87	— .6	Apex, one finger outside nipple, marked tachycardia.
16	....	10½	126	9.5	9.4	+ .1	No symptoms or signs.
17	....	12	131	10.1	9.87	+ .2	No symptoms or signs.
18	....	11	130	10.9	9.4	+1.5	No symptoms or signs.
19	....	13	141	10.	10.39	— .39	No symptoms or signs.
20	....	13	157	8.4	12.5	—4.1	No symptoms or signs.
21	....	10	121	10.2	9.4	— .8	No symptoms or signs.
22	....	12	128	8.6	9.4	— .8	No symptoms or signs.
23	....	9½	121	9.5	9.4	+ .1	No symptoms or signs.
24	....	12	126	9.4	9.4	.0	No symptoms or signs.
25	....	9	117	8.4	8.82	— .4	No symptoms or signs.
26	....	12	142	10.7	10.39	+ .3	No symptoms or signs.
27	....	8	112	8.7	8.82	— .1	No symptoms or signs.
28	....	11	152	10.5	11.3	— .8	No symptoms or signs.
29	....	10	132	8.5	9.87	—1.3	No symptoms or signs.
30	....	15	145	8.9	10.39	—1.4	No symptoms or signs.
31	....	11	135	8.7	9.8	—1.1	No symptoms or signs.
32	....	14	155	8.8	12.5	—3.8	No symptoms or signs.
33	....	10	132	9.1	9.87	— .7	No symptoms or signs.
34	....	12	140	8.8	9.87	—1.0	No symptoms or signs.
35	....	5½	94	7.7	8.4	— .7	No symptoms or signs.
36	....	13	130	8.6	9.4	— .8	No symptoms or signs.

*The first fifteen cases in this table are those in which symptoms or physical signs of cardiac abnormality were present. The remainder were free from such signs.

discrepancy, though in so small a number of cases, is important enough to deserve further investigation.

Returning once more to our own cases, we have placed the children who show either subjective or objective signs of cardiac involvement together at the commencement of Table 1. (Cases 1 to 15.) In the last column are enumerated the corresponding signs and symptoms.

A study of these fifteen cases shows that in none of them is the heart increased in size. Two of them reveal an increase over the normal of 2 and 3 mm., respectively, values which, as was mentioned above, are within the limits of error. On the other hand, nine of the remaining show a distinctly small heart, differing in one case by as much as 22 mm. from the normal size. The hearts are enlarged neither to percussion nor to fluoroscopy, with four exceptions (Cases 8, 9, 14 and 15), in which percussion showed slight enlargement to the left, which was verified, however, by the orthodiagraph only in one instance. The significance of the enlargement in this case (Case 9) will be discussed later. Our results are, therefore, in accord with the observations of Langstein, Reyher and Fischl, who found no enlargement.

In spite of the absence of any demonstrable increase in the size of the hearts, all of these children nevertheless had definite symptoms. They commonly complained of dyspnea on exertion, of palpitation, or more rarely, of precordial pain. Twelve of the fifteen had definite signs of abnormal function; five had booming first sound; three had apical systolic murmurs; four had marked accentuation of the second pulmonic sound; four showed apical signs of marked over-action and four showed increase of heart dulness to the left. These are all distinct signs and symptoms of relative heart insufficiency, and undoubtedly correspond to the cases described by Martius and others as dilatative weakness.

It may not be amiss at this point to present in detail the history and physical examination of one of our cases:

History.—R. P. (Case 8), female of Russian parentage, aged 10 years.

Family History.—An older sister has rheumatic endocarditis for which she has been in the hospital on several occasions. Parents well. No history of tuberculosis.

Past History.—Measles in early childhood. Except for several mild attacks of tonsillitis the child has been well. Has never had scarlet fever.

Present Illness.—For the past ten months the patient has noted epigastric oppression, severe dyspnea and palpitation on exertion. No cough. No sweats. No edema. No fever. Does not vomit. Appetite fair. Bowels regular. Sleeps well.

Physical Examination.—A very nervous child, showing poor muscular tonus, as evidence of which there is a marked exaggeration of the lumbar lordosis. Marked pallor of the skin, but lips and mucous membranes strikingly ruddy. Hands cold and cyanotic. Marked dermographia. Chvostek's sign positive.[14]

14. For the value of this sign see Bass, "Chvostek's Sign and Its Significance in Older Children," Am. Jour. Med. Sc., July, 1912.

Mouth, throat, lymph-nodes, eyes negative. Chest long and flat; scapulae winged: epigastric angle narrow. Lungs negative. Heart: Apex in the fifth space in the nipple line; distinct over-action; percussion shows the left border one finger outside the nipple line; first sound at apex booming in character; no murmurs; second sounds at base accentuated; action regular, somewhat rapid; short venous hum over the vessels of the neck; pulses regular; no increased tension. Abdomen lax; right kidney palpable.

Orthodiagraphy reveals a heart normal in shape, size and position.

Urine: A. M. specimen albumin-free; p. m. specimen, faint trace of albumin; after lordosis (kneeling for three minutes), very heavy precipitate of albumin.

This case, then, presents the typical picture we have above described—a child who comes to us complaining of severe palpitation and dyspnea on exertion, who is suffering from orthostatic albuminuria, whose physical examination by the ordinary methods would lead one to suspect cardiac enlargement. However, in spite of the signs of cardiac over-action and the fact that percussion shows the heart dulness one finger to the left of the nipple, careful measurement with the orthodiagraph proves that the heart is normal in size and position.

It may be concluded from our findings that the conception "dilatative weakness" as applied to cases of orthostatic albuminuria, at least in so far as it assumes enlargement of the heart, is a mistaken one, due probably to errors in percussion, which will be discussed later on. Nor can the small hearts stand in a causative relation to these symptoms, since the smallest heart sizes were found among those children who did not present any symptoms at all.

EXAMINATION OF HEART SIZE AFTER EXERTION

Having definitely decided that these hearts during rest were normal or under-sized, the next question to be determined was what alteration in size, if any, the heart underwent after exercise.

The change in size in the normal heart after exertion has been thoroughly studied by numerous observers since the introduction of precise methods for the determination of heart size. Moritz,[15] Dietlen,[16] Kienbock,[17] Agostini,[18] Jundell and Sjögren[19] and many others showed that contrary to the previously current opinions, the normal heart, even after exhausting exercises, contracts considerably in volume. It follows from their work that acute dilatation of the healthy heart does not occur. Martius, quoted by Langstein,[2] however, believes that cases of dilatative weakness previously referred to react to exertion by an increase in heart size, and therefore concludes that these hearts are weak. According

15. Moritz: München. med. Wchnschr., 1907, No. 14; also 1908, No. 25.

16. Dietlen: Ergeb. der Physiologie, 1910; also München. med. Wchnschr., 1907, No. 10.

17. Kienbock, Selig and Beck: München. med. Wchnschr., 1907, No. 29.

18. Agostini: Ztschr. f. exper. Pharm. u. Therap., 1909, p. 159.

19. Jundell and Sjögren: Reviewed in Centralbl. f. inn. Med., 1912, No. 42, p. 1053.

to Martius, this symptom is one of the most frequent in orthostatic albuminuria.

Schaps,[12] relying on percussion, in an examination of sixteen cases of orthostatic albuminuria showing cardiovascular symptoms or signs, found only one case in which after exercise the heart seemed to have enlarged. This is of particular interest, in view of the fact that of the thirty-five cases described by him, twenty showed pathological heart findings (murmurs, arhythmia, accentuation of the basic sounds, instability of the pulse).

Neumann[20] in eight cases of dilatative weakness, two of which had albuminuria, found by percussion that after stair-climbing the hearts increased in size.

TABLE 2.—SHOWING HEART SIZE BEFORE AND AFTER EXERCISE IN CASES OF ORTHOSTATIC ALBUMINURIA*

Case	Transverse Diameter Before Exercise, cm.	Same after Exercise, cm.	Difference, cm.	Case	Transverse Diameter Before Exercise, cm.	Same after Exercise, cm.	Difference, cm.
1	8.2	7.9	— .3	19	10.	9.3	— .7
2	8.6	8.3	— .3	20	8.4	8.4	— .0
3	8.4	8.2	— .2	21	10.2	9.7	— .5
4	8.7	8.3	— .4	22	8.6	8.2	— .4
5	8.2	8.3	+ .1	23	9.5	9.4	— .1
6	9.4	8.8	— .6	24	9.4	9.3	— .1
7	9.1	9.1	— .0	25	8.4	7.9	— .5
8	9.1	9.1	— .0	26	10.7	10.4	— .3
9	9.6	9.6	.0	27	8.7	8.	— .7
10	8.2	8.1	— .1	28	10.5	9.9	— .6
11	8.7	8.6	— .1	29	8.5	8.4	— .1
12	7.8	7.8	.0	30	8.9	8.6	— .3
13	9.1	8.9	— .2	31	8.7	8.7	— .0
14	10.	9.2	— .8	32	8.8	8.4	— .4
15	9.3	9.1	— .2	33	9.1	8.8	— .3
16	9.5	9.3	— .2	34	8.8	8.1	— .7
17	10.1	9.7	— .4	35	7.7	7.6	— .1
18	10.9	10.4	— .5	36	8.6	?	?

*This chart shows the heart-size before and after exercise. As in chart one the first fifteen cases are those with cardiovascular symptoms or signs.

The work of these observers is, however, not beyond criticism, since they relied for the determination of heart size on percussion only. We have been unable to find records of any orthodiagraphic heart examinations before and after exercise, either in cases of orthostatic albuminuria or in cases of dilatative weakness, and consider such an examination absolutely necessary for a conclusive determination of the question of dilatation after exercise. Such examination we have carried out. The exercise consisted in rapidly running up and down 160 steps, which

20. Neumann: Jahrb. f. Kinderh., 1900, lii.

always resulted in considerable fatigue. The children were then immediately examined on the fluoroscope and orthodiagraphic tracings made under exactly the same conditions and position in which the tracings had been made before exercise.

Table 2 shows in parallel columns the transverse heart diameters in our thirty-six cases before and after exercise. It will be seen that in twenty-two cases the heart became distinctly smaller, while in the rest of the cases it remained unchanged or practically so. In no case did the heart become larger after exercise, not even in the children showing subjective or objective cardiac symptoms. These results definitely prove that the cardiac symptoms in this undoubtedly clinically distinctive group must find an explanation elsewhere than in the altered heart size, possibly in some disturbance in the vasomotor system.

It is noteworthy that although none of the hearts increased in size, thirteen of them failed to grow smaller.[21] (We have included those which diminished only 1 mm., as this was practically no change in heart size.) The failure of these hearts to contract after exercise is the more remarkable and is indicative of some abnormality of heart action, in view of the experience of Moritz that the hearts of youthful individuals and of those who are not accustomed to hard work, show the greatest amount of contraction. The exact significance of this fact we are not in a position to state; it may be looked on as an evidence of abnormal cardiac response, as healthy hearts quite regularly show a distinct diminution in size after exercise.

Various explanations have been advanced to account for the discrepancy between the increased size of the heart as shown by percussion and the actual findings as shown by the more objective methods. Herz,[22] Romberg,[23] Hoffman[24] and other authors have cautioned against the fallacy into which one is easily led, especially in cases of overacting hearts where the force and transmission of the apical impulse to the left, or as some describe it, its "irradiation," give the impression of cardiac enlargement. One is more prone to make such an error in cases with narrow, flat chests in which the heart has perhaps assumed a position absolutely nearer to the axilla because of lessened capacity of the thorax, and in which for the same reason the apex-beat has acquired a more lateral position in relation to the nipple. In addition, on exertion, with its resultant dyspnea, a transitory emphysema is produced whereby the diaphragm is pressed downward, pulling with it the apex of

21. In the estimation of heart size we have utilized the transverse diameter of the heart rather than the superficial heart area, as recommended by Moritz and Dietlen, owing to the errors inherent in the latter method.

22. Herz: Med. Klin., 1903, p. 778.

23. Romberg: Deutsch. med. Wchnschr., 1908, No. 47.

24. Hoffman: Kongress f. inn. Med., 1902, xx.

the heart, thus creating the impression of enlargement, which is in fact only a displacement. These observations have special point in connection with orthostatic albuminuria, in which all observers who have used the *x*-ray for determination of heart size have without exception failed to find the heart enlarged, as opposed to those who by percussion frequently found the opposite. A concrete example in one of our cases will illustrate this liability to error:

Case 4 is a boy aged 14 years, tall, rapidly growing, with the flat, narrow chest which we have found so frequently in these cases, and which appears to be accentuated at puberty. Careful examination shows an overacting heart, a somewhat diffuse apical impulse, heaving in character, the left border percussing one finger outside the nipple line.

Such a heart might on purely clinical grounds be considered enlarged. An orthodiagram, however, reveals a heart normal in shape and size, but one which, owing to the narrowness of the chest, appears to occupy more space than is allotted to the heart in a chest of normal capacity; it therefore appears nearer the axilla, the heart being relatively too large for the thorax. Exactly similar conditions obtain in Case 8, a tall narrow-chested 10-year-old girl. The same explanation will apply to our finding so many small hearts; they are absolutely smaller for the height of the child, but relatively to the narrow chest they are normal in size.

THE JUVENILE HEART

It appears, therefore, that the foregoing results fail to disclose any evidence of cardiac enlargement in the great majority of cases. The few exceptions, however, to one of which reference was made in an earlier part of this article, are worthy of careful consideration, because they illustrate a definite heart type which, both as to morphology and function, stands in marked contrast to the rest of our cases. These are Cases 9, 17 and 18.

Although only one of these (Case 18) shows orthodiagraphically a definite enlargement of the heart, there is undoubted evidence of left ventricular hypertrophy in all of them. Viewed on the fluoroscopic screen one is immediately impressed by the deliberate forcible pulsation of the left ventricle, by the rounded blunt apex and by the transverse position and oval shape which the heart has assumed (see Fig. 1 and compare with Fig. 2). These are all classical signs of left ventricular hypertrophy, combined in Case 18 with moderate dilatation. What is the significance of these changes in heart action and shape?

Under the name of *"Wachstumshypertrophie"* or juvenile heart, Krehl[25] has described a type of case in which an enlarged heart occurs at or about the age of puberty, in the absence of nephritis or other

25. Krehl: Nothnagel's System, xv, 391.

usual cause of left ventricular hypertrophy. In a large series of boys he was able to find a number in whom the heart was enlarged to percussion. In others in whom no enlargement was demonstrable, there was distinct evidence, however, in the heaving impulse and in the accentuated basic sounds, of left ventricular hypertrophy. In those cases in which the apex impulse was not heaving, although the heart percussed beyond the nipple, it was assumed that dilatation predominated over hypertrophy. Some of these cases had subjective symptoms, others had none, but in Krehl's experience their presence in every instance was associated with the heart changes described.

Our three patients above referred to, only one of whom complained of any subjective symptoms, correspond well to the Krehl type. They

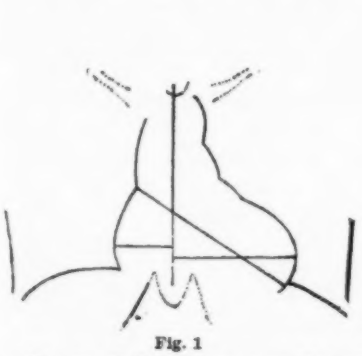

Fig. 1

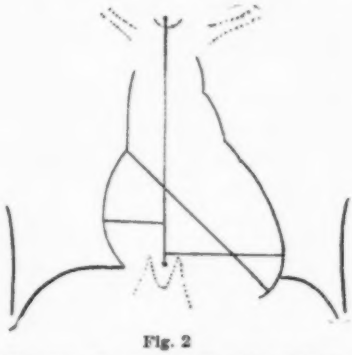

Fig. 2

Fig. 1.—Orthocardiogram of "Juvenile Heart." Transverse diameter 1.5 cm. greater than normal. Shows transverse position, rounded apex, and deliberate, powerful pulsation characteristic of left ventricle hypertrophy.

Fig. 2.—Orthocardiogram of normal heart.

comprise a group in which probably only transitory heart changes occur, dependent on the disproportionate development of the circulatory organs and the rest of the body. In some cases this leads to an efficient hypertrophy; the heart being equal to the increased demands made on it. In others this hypertrophy is insufficient and subjective symptoms develop.

We are still more assured that these three cases correspond to the juvenile heart of Krehl, from the observations of Schwartz.[26] The latter has made orthodiagraphic tracings of these hearts and insists that the fluoroscopic appearance above described is characteristic of this condition, and that by this means only can it be definitely diagnosticated. This is a point worthy of emphasis. By the ordinary methods of heart

26. Schwartz: In von Jagic's Handbuch der Herz und Gefässerkrankungen, Vienna, 1912, p. 436.

examination the pure hypertrophy without cardiac enlargement in these cases might easily be overlooked, whereas the above-described characteristic heart silhouette effectively decides the diagnosis.

EXAMINATION OF HEART RATE AFTER EXERTION

All who have written on the subject of orthostatic albuminuria are agreed that in the cases characterized by cardiovascular disturbances, the most constant feature is the variability of the pulse, its so-called "labil-ity" (instability). By this term (German *"Labilität"*) is understood the tendency of the pulse to become much more rapid and poor in quality after very slight exertion. In cases showing this phenomenon, after simple exercise, as running up and down a few flights of stairs, it may be impossible to count the pulse at the wrist, owing to its extreme rapidity and smallness. In its most marked form, change in posture

TABLE 3.—PULSE RATE RECUMBENT, STANDING AND AFTER EXERCISE IN CASES OF ORTHOSTATIC ALBUMINURIA*

Case	Pulse Rate in Recumbent Position	Pulse Rate Standing	Pulse Rate after Exercise	Case	Pulse Rate in Recumbent Position	Pulse Rate Standing	Pulse Rate after Exercise
1	68	72	124	16	72	80	144
2	78	80	100	17	68	72	136
3	92	92	184	18	120	120	148
4	92	96	160	20	112	124	156
5	76	76	72	22	76	88	84
6	80	100	152	23	84	100	88
7	78	86	128	25	100	100	96
8	88	100	108	26	80	84	100
9	88	88	132	27	80	80	160
10	96	104	144	30	120	120	120
11	80	84	148	31	88	96	132
12	96	120	172	32	80	112	150
13	100	104	?	33	80	88	96
15	140	140	195	34	80	80	168

*Cases 1 to 15 are those which show cardiac symptoms or physical signs.

from the recumbent to the upright is said to result in a disproportinate rise in pulse-rate. To this symptom Thomayer gave the name "orthostatic tachycardia." Fischl[13] found this instability to be an almost constant symptom, the pulse becoming smaller and more rapid by 25 to 30 beats, while Pelnar[27] in sixteen cases was able at times to note an actual doubling of the pulse-rate. The effect on the pulse of the change of position from the horizontal to the upright is of special interest, because the albuminuria in these cases is so closely related to posture.

In Table 3 in the first column are given the pulse-rates in the reclining position. The rates resulting from a change to the upright position are seen in the next column. These figures show in the first place

27. Pelnar: Centralbl. f. inn. Med., 1905, p. 1025.

that practically all the patients have approximately normal heart-rate when resting. The increase in rate on standing in the entire group varied between 0 and 32 (average 7). In the cases showing cardiovascular disturbances the increase varied from 0 to 24 (average 7). It will be seen that the cases showing symptoms differ in no wise from the remainder of the group of albuminurics. We have as a control examined the pulse-rates in ten perfectly healthy normal children 9 to 14 years of age, and found that the rate after changed positions was increased from 0 to 16 beats (average 8.4); in other words, slightly greater increase than in albuminurics. The increase in rate in our cases of albuminuria can therefore in no manner be considered excessive.

There are also numerous figures available for comparison in the literature: Dietlen[28] in adults finds a normal variability of 8 to 40 beats, with an average of 18; Guy[29] found a range of 4 to 44 and Shapiro[30] 10 to 30 beats. It is therefore evident that our cases do not show any marked instability on change of posture. We have no doubt that unusual environment and the nervousness attendant on it, which we have taken pains to eliminate, can easily lead to error, as those hearts which at rest are unduly rapid show a proportionate increase on change of posture.

In the third column of Table 3 are tabulated the pulse-rates after exercise, which consisted in running up and downstairs, as noted before. The average increase in the cases with cardiac disturbance is 48 beats per minute, whereas, in the remainder the pulse-rate increased but 22 beats per minute. Results such as this would at first glance seem to point clearly to an abnormal irritability of these hearts and would seem to correspond well with the description given by the Germans to cases of pulse instability. However, when we examined the pulse-rates in perfectly normal children used as controls, we were much surprised to find that in them the increase in rate even exceeded that occurring in the orthostatic albuminuria cases, the healthy children showing an average increase of 50 beats per minute. Mere numerical increase in pulse-rate, therefore, cannot be taken as a criterion of instability in these cases.

From all the foregoing it might be suspected that our cases are in reality not of the same class as described by Martius as dilatative weakness, since we have shown that both as to heart size and pulse-rate our results are not in accord. However, when we take into account the character of the pulse before and after exertion, and especially when we compare the pulse with the cardiac action, both as evident to inspection and to the *x*-ray, we are impressed by the fact that our cases and those of Martius are the same. A large percentage of our patients after run-

28. Dietlen: Deutsch. Arch. f. klin. Med., 1909, xcvii.
29. Guy: Guy's Hosp. Reports, 1838.
30. Shapiro: Wratsch, 1881 (quoted by Dietlen).

ning the stairs presented a characteristic picture of extreme fatigue and dyspnea. The pulses, which had previously been fairly strong, became weak and thready, so that in several instances the pulse could not be counted at the wrist. At times irregularity of the pulse also occurred. Not only was the apex impulse in many of these children with weak pulses extremely forcible, but the *x*-ray revealed markedly overacting hearts. This paradoxical condition of pulse and apex, which has been so frequently emphasized by European observers, therefore appears to be a characteristic symptom of this condition.

EXAMINATION OF THE SHAPE OF THE HEART

Aside from the information we have acquired concerning the size and functional capacity of the heart, *x*-ray study of our cases has revealed some interesting features concerning heart shape. It is well known from

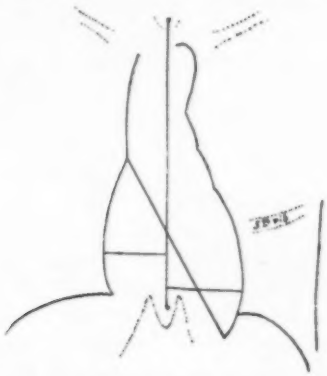

Fig. 3.—Orthocardiogram of "Drop Heart." Transverse diameter 8.8 cm. Normal is 12.5 cm. Note position of fifth rib.

the works of Veith and Reyher[31] that the commonest form of the heart silhouette in childhood is that of an obliquely placed oval (Fig. 2); less commonly hearts of a rounded shape occur; and still more rarely the heart assumes either a transverse or a vertical position. The study of the heart shape in our cases shows in quite a number a striking deviation from this normal type. This abnormality consists in the tendency that the hearts show to assume a more median position in the chest, the apex of the organ appearing relatively lower, thus causing a vertical position of the heart axis. This gives the heart a drawn-out, narrow appearance, which, coupled with the elongation of the great vessels, results in a distinctive heart picture which has been aptly termed by the Germans the drop heart (*Tropfenherz*). This condition (Fig. 3), or one closely

31. Reyher: Jahrb. f. Kinderh., 1906, lxiv.

approaching it, we have found in ten of our cases, about 30 per cent., contrary to the report of Fischl,[13] who was unable to find such hearts in cases of orthostatic albuminuria.

The drop heart has for many years been well known to the Germans, especially through the writings of Kraus,[32] by whom it has been associated with narrow-chested individuals, showing the neurasthenic habitus, who reveal various stigmata of constitutional weakness in which the heart is supposed to participate. Our findings, therefore, of such a large percentage of vertical or drop hearts is of particular interest, in view of the fact that it occurs in the very type of child which Martius has characterized as constitutionally weak.

CONCLUSIONS

Reviewing briefly the results of our investigations, we believe the following conclusions are warranted:

1. In a series of cases of orthostatic albuminuria selected at random, it will be found that a considerable number present evidence of relative cardiovascular insufficiency.

2. These symptoms, in the great majority of cases, are not associated with any hypertrophy or dilatation of the heart. On the contrary, the heart is in many cases smaller than normal; nor does it show any gross evidence of weakness as dilatation after exercise, an explanation suggested by previous investigators.

3. Although the hearts do not dilate after exercise, a considerable number of them fail to become smaller under these conditions. This failure to contract may perhaps be looked on as a restriction of the field of cardiac response.

4. The condition known as the juvenile heart or *"Wachstumshypertrophie"* occurred three times in our cases and can be distinctly recognized.

5. The conception of pulse or heart instability must be restricted to a tendency of the pulse to become smaller and impalpable after exercise, a condition which we have found very common.

6. In 30 per cent. of the cases we have found hearts of the drop type, especially associated with other stigmata of constitutional maldevelopment.

In conclusion we wish to express our thanks to Dr. Leopold Jaches of the *x*-ray department of Mount Sinai Hospital for numerous courtesies extended to us during the course of our work.

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32. Kraus: Med. klin., 1905, No. 50; also Gedenkschrift für von Leuthold, 1906.

A PRELIMINARY REPORT ON THE EFFECT OF STRYCHNIN AND DIGITALIS ON MAN *

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It is not the object of this article to enter into a discussion of the effect of strychnin or digitalis on the systems of the body as observed on the lower animals, or to go over the literature on the subject, but to report observations when these drugs were administered in therapeutic doses to normal young men.

Before entering on a report of the findings, I desire to call attention to the fact that text-books on pharmacology and highly scientific articles pertaining to this subject are based largely on experimental evidence furnished by the lower animals. This evidence has been and is of inestimable value in determining the presence and the location of an effect and establishes a valid reason for a continuance of the experimental work by making observations on the higher animal, man.

In a very few instances observations have been made on the normal man and the effect as seen has been reported. In nearly all cases, however, such observations have been on a single case or on a number of such cases under different conditions, thus making the results of little value. It is only when conditions are identical that a composite curve becomes of value. I question the advisability of accepting in all cases the evidence of an effect on respiration, pulse and blood-pressure furnished by the lower animals as satisfactory proof of a similar action in man. I have arrived at this conclusion after careful observations of the effect of some of our most important drugs on groups of men and a comparison with the scientific findings on animals.

I am inclined to believe that this may be the main reason why pharmacologists and clinicians have held opposite views regarding important drugs, the pharmacologist furnishing conclusive scientific proof of action as based on the lower animals, while the clinician has failed to furnish the necessary scientific proof on the diseased man.

I think that the time is at hand when pharmacologists should establish scientific proof of the effect of important drugs when administered in different doses on the normal man, not that we can infer that a similar action must necessarily follow in the diseased man, but, from the

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*From the Department of Pharmacology, College of Medicine, University of Vermont.

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evidence thus furnished, we will be in the best possible position to study the effect on the diseased man, compare the results and determine wherein they differ. Until this evidence is forthcoming we cannot expect that pharmacology will be placed on a highly scientific basis.

STRYCHNIN

Strychnin and digitalis are two important drugs, the effect of which seems to have been in doubt, as voiced by both pharmacologists and

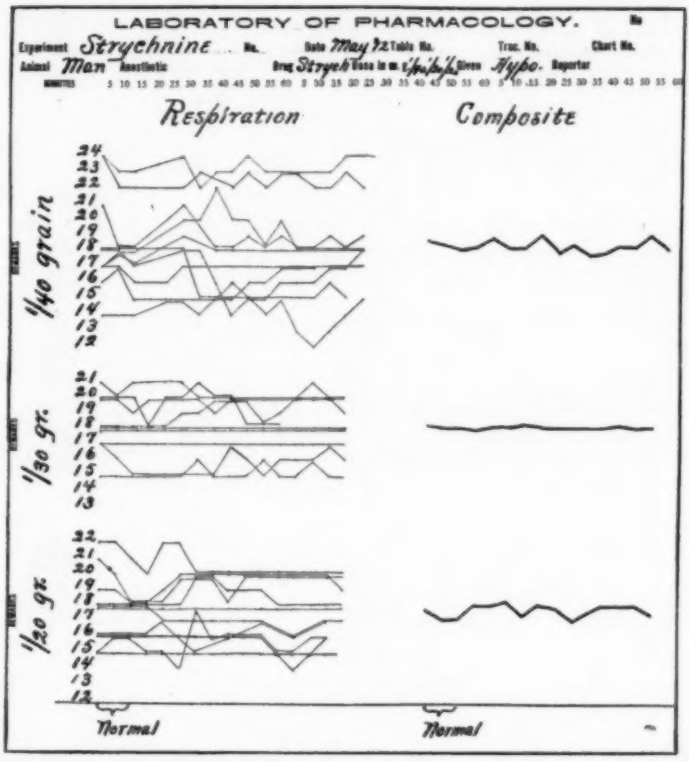

Chart 1.—Curves showing the effect at various time intervals of strychnin in different doses on the respiration.

clinicians, the majority of pharmacologists claiming that strychnin and digitalis do not increase blood-pressure while some clinicians claim to have seen such effect. In view of this fact and the desire to add to the evidence, I submit the following observations made on groups of medical students in the University of Vermont who willingly volunteered their services. Selection was made to exclude those who were under the

influence of nicotin. They were all seated at tables in the laboratory and remained very quiet throughout this entire experiment, thus making the conditions identical. About twenty minutes were allowed to elapse before beginning observations, thereby permiting respiration, pulse and blood-pressure to return to normal. Three normal observations were then taken. The respiration and pulse were taken by students of the section who were not taking the drug, while the blood-pressure in all cases was taken by my assistant or myself.

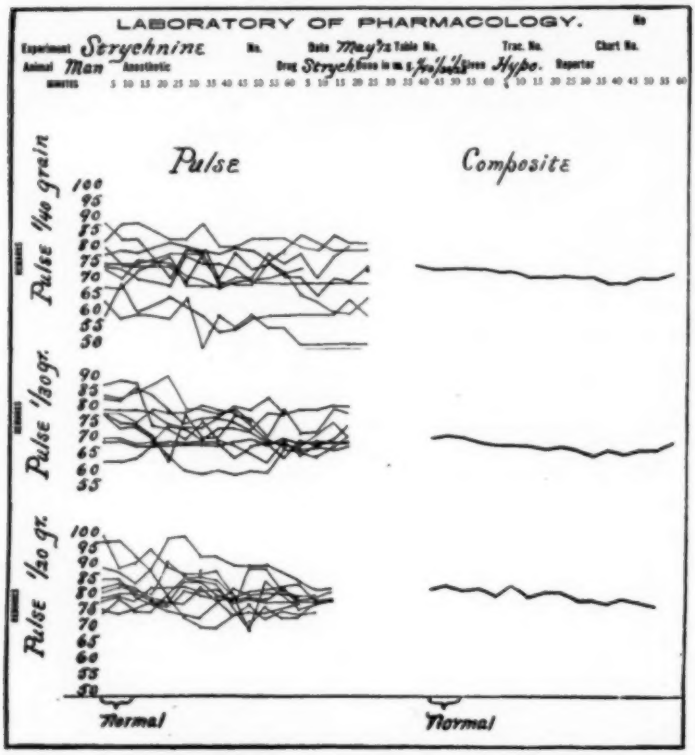

Chart 2.—Curves showing the effect at various time intervals of strychnin in different doses on the pulse-rate.

After completing the normal observations, strychnin sulphate was injected by hypodermic into the muscular tissue of the upper arm. Observations were then made every five minutes on respiration and pulse and every ten minutes on blood-pressure.

These experiments were conducted on three different days, each time using a different dose of strychnin sulphate.

June 3, 1912, at 9:13 a. m., ten men of Section A received 1/20 grain.

June 5, 1912, at 11:25 a. m., ten men of Section B received 1/30 grain.

June 22, 1912, at 11:15 a. m., ten men of Section B received 1/40 grain.

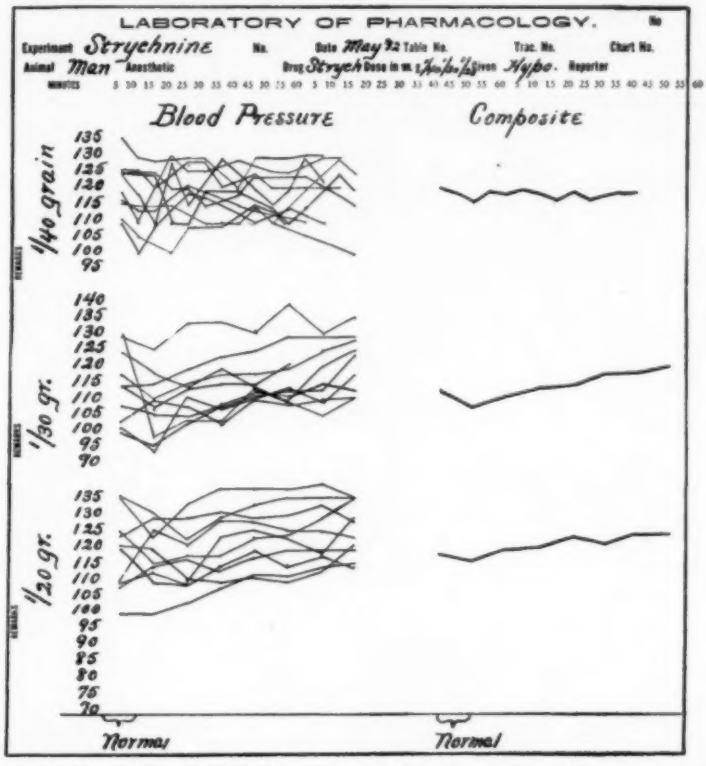

Chart 3.—Curves showing the effect on blood-pressure of different doses of strychnin.

Nearly all who received 1/40 grain were men who did not receive the drug on June 5.

The result of these experiments seems to indicate that strychnin in doses of 1/40, 1/30 and 1/20 grain has no appreciable effect on the rate of respiration (Chart 1). There is an average slowing of the pulse-rate of five beats per minute from 1/40 grain, seven beats per minute from 1/30 grain and eight beats per minute from 1/20 grain (Chart 2). The maximum effect from 1/40 and 1/30 grain seems to have been reached

at the end of forty minutes, while from 1/20 grain the composite curve shows a downward tendency at the end of the experiment.

The blood-pressure curve, taking the last normal observation as our standard, shows an increase of about 3 mm. of mercury from 1/40 grain, 13 mm. from 1/30 grain and 8 mm. from 1/20 grain.

It will be noted from the graphic chart (Chart 3) that there was a slight increase in blood-pressure from 1/40 grain, a pronounced increase

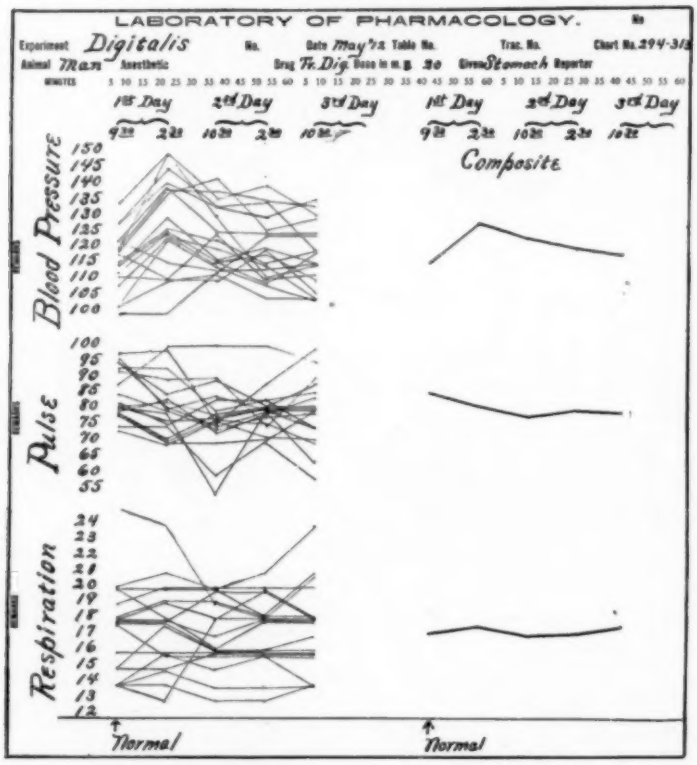

Chart 4.—Curves showing the effect of digitalis on respiration, pulse and blood-pressure.

from 1/30 and 1/20 grain and at the end of the experiment, the blood-pressure was increasing.

I believe that this evidence, obtained from thirty observations with varying doses, is conclusive proof that strychnin, when given in the above doses by hypodermic injection, does increase blood-pressure in the normal man.

A former series of similar experiments conducted in like manner, with the exception of the method of administration, the strychnin being given under the tongue, produced identical results. The duration of effect was shorter, the blood-pressure returned to normal in forty minutes from 1/30 grain and in one hour from 1/20 grain.

DIGITALIS

From experiments on groups of men conducted in like manner as in the strychnin experiments, we have failed to obtain any effect on the rate of respiration or pulse or any change in blood-pressure during one hour and twenty minutes following the administration of tincture digitalis.

The doses were 10, 15 and 20 minims, given by stomach.

These results were anticipated from the knowledge of the active principles present in digitalis and the consensus of opinion as to the time after its administration before an effect is supposed to occur.

Having thus failed, we determined to conduct an experiment with a group of men, taking observations twice each day. The object of this experiment was, first, to establish the presence of an effect, if any, from a single dose, and second, if an effect was noticed, to determine how long it continued.

The preparation used during these experiments was a fresh tincture made from Allen's English leaves on April 12, 1912, by W. H. Zottman & Co. of this city. After obtaining results from this tincture, I desired that it be standardized by a disinterested person, using the same methods as are used by the large manufacturers. Mr. P. S. Pettenger of the H. K. Mulford Co. kindly volunteered to standardize it on guinea-pigs, which he did, finding it to be a 6.9 per cent. tincture. From this we conclude that the dose of 20 minims given was equivalent to about 14 minims of a standard tincture. Therefore the results obtained should be considered as produced by 14 minims instead of 20.

A group of men were selected on May 20, 1912, under similar conditions as in the strychnin experiments, and, after obtaining the normal observations, they were given at 9:30 a. m. 20 minims of the above tincture digitalis.

At 2:30 p. m. on the same day, after this group had listened to a lecture for one period, and, from previous instructions, had remained quiet in their seats, observations were repeated on respiration, pulse and blood-pressure.

These observations were repeated on May 21, in the same room and under identical conditions, at 10:30 a. m. and 2:30 p. m.; also on May 22 at 10:30 a. m.

The observations on respiration and pulse were made by students, while all observations on blood-pressure were made by myself.

A change in the schedule of this group on the afternoon of May 22 interfered and observations were not made until May 23 at 10:30, when

the average blood-pressure was found to be normal. This last observation is excluded from the graphic chart.

After a careful study of our findings, I determined to repeat the experiment under similar conditions, but with a different group of men and have Dr. Bush, my assistant, take all observations on blood-pressure, that he might disprove or verify my findings. This was done on May 27, 28 and 29.

The results from this group were found to correspond with our first group, as will be seen from the graphic chart which represents all observations (Chart 4).

It will be noted that an average increase in blood-pressure of 13 mm. Hg occurred, which reached its height in five hours, and that it did not return to normal until after fifty hours had passed.

This increase occurred in seventeen out of eighteen cases, and in thirteen the greatest effect was noticed at the end of five hours, thus proving that the old idea of the maximum effect appearing in twenty-four hours is erroneous.

A slowing in the pulse of eight beats per minute was obtained with practically no effect on rate of respiration.

Controls were used in all these experiments, which show little or no variation from a straight line. Such slight variation as occurred did not conform to the composite curve showing drug effect.

I regret that the strychnin experiments were not conducted over a longer period of time, that the maximum height in blood-pressure and its duration could have been determined, but this was made impossible by our schedule. It is my purpose to conduct further experiments in the near future with this idea in view.

SUMMARY

STRYCHNIN

No effect on the rate of respiration, except from 1/20 grain, which produced an average increase of one per minute. This effect was not constant, a drop occurred occasionally, which was due largely to individual fluctuations occurring at the same time and without apparent cause.

A slowing of the pulse-rate from all doses.

A marked increase in blood-pressure from 1/30 and 1/20 grain. Practically no effect from 1/40 grain.

DIGITALIS

No effect on the rate of respiration.

A slowing in the pulse-rate of eight beats per minute.

A marked increase in blood-pressure which reached its maximum in five hours, gradually returning to normal after fifty hours.

A persistence of action for fifty hours from a single dose of 14 minims of a standard tincture digitalis.

HUMAN BOTRYOMYCOSIS OF THE LIVER*

EUGENE L. OPIE, M.D.
ST. LOUIS

The disease of horses subsequently known as botryomycosis was first described by Bollinger[1] in 1870. He found multiple grayish-white fibrous nodules in the lung of a horse. Areas of softening occurred within the nodules and in the pus were yellow white granules which were just visible and resembled the yellow granules of actinomycosis. Examined under the microscope these granules do not exhibit the characteristic appearance of the "ray fungus," but are composed of coccus-like bodies surrounded by a homogeneous medium, which, regarded as a capsule, collects the microorganism into a zooglea mass. On the surface of the granule are rounded projections which give it a mulberry-like form. A disease characterized by the presence of this microorganism is not uncommon in horses and in some countries, particularly in the tropics, affects the human skin. The disease in man has not been described in this country and in none of the instances observed elsewhere has it attacked an internal organ.

Botryomycosis is described in text-books of veterinary medicine.[2] It occurs occasionally in cattle and swine. Several writers make the statement that actinomycosis is not uncommon in cattle and infrequent in the horse, whereas, the similar lesion of botryomycosis is frequent in the horse and uncommon in cattle. Firm nodules are formed in the skin, particularly in regions where it is subjected to continued rubbing of the harness; for example, below the collar, and after the skin has broken and pus is discharged, infection is transferred to other parts of the skin exposed to like friction, the microorganism being, presumably, rubbed into the ducts of cutaneous glands. Infection of wounds occurs and the development of a slowly growing fibrous tumor or botryomycoma has been repeatedly observed in geldings at the site of the cut end of the spermatic cord. Botryomycosis occurs in organs not obviously exposed to infection, for example, the udder.

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* Accepted for publication in THE ARCHIVES, Jan. 31, 1913.

* From the Department of Pathology, Washington University Medical School, St. Louis.

1. Bollinger: Mycosis der Lunge beim Pferde. Virchows Arch. f. path. Anat., 1870, xlix, 583.

2. Hutyra and Marek: Pathology and Therapeutics of the Diseases of Domestic Animals (Translation). Chicago, 1912; Kitt: Lehrbuch der pathologischen Anatomie der Hausthiere. Stuttgart, 1906-1910.

The newly-formed mass of fibrous tissue is usually situated in the subcutaneous tissue, but may extend into the muscles. Tumor-like masses, weighing from 30 to 60 pounds, are described. The lesion arising at the cut end of the spermatic cord may extend along the inguinal canal to the peritoneum. The swelling consists, in large part, of dense fibrous tissue, but all the elements of an infectious granuloma, including epithelioid and giant cells, are represented. Formation of pus occurs particularly about the colonies of microorganisms, and fistulous suppurating canals often penetrate the lesion and open on its surface. Numerous nodules may be formed in the skin near the primary lesion. Regional lymphatic nodes may enlarge and form foci of suppuration, but more frequently the lymphatics and lymphatic nodes are unaffected.

Botryomycosis of the horse occasionally occurs in the internal organs and is usually secondary to infection of the skin or of a wound. Primary botryomycosis of internal organs has been observed rarely. Secondary nodules have been found in the kidneys, liver and spleen, in bones and in other organs usually in association with infection of the spermatic cord. Simultaneous development of the lesion in a number of organs has been observed in several instances.

Peculiar to botryomycosis are the minute yellowish-white lobulated or mulberry-like granules composed of cocci held together by a homogeneous material which is often conspicuous as a clear layer at the periphery of the body, the whole having the appearance of a colony of micrococci. W. Ernst[3] points out that the smallest masses of cocci are not surrounded by the encapsulating material which stains with acid dyes such as eosin or picric acid, but form this material at a later stage. The rounded projections on the surface of these bodies giving them their mulberry-like form are produced by multiplication of cocci within the capsule, distending and rupturing it at certain points, for in favorable sections he found bacteria uncovered by the homogeneous material projecting through this otherwise intact medium.

To the peculiar colony-like structure which has been described, Bollinger, finding it in the lung, gave the name *Zooglea pulmonis equi.* Rivolta[4] subsequently rediscovered the same microorganism in a tumor from the cut spermatic cord of a horse, and considering it analagous to *Actinomyces,* gave it the name *Discomyces equi.* Johne[5] found the microorganism in a fungoid growth from the spermatic cord of a horse and in nodules of the skin, and recognizing its coccus form, called it *Micrococcus ascoformans.* In 1886, Rabe[6] first described cultures and inoculation

3. Ernst, W.: Centralbl. f. Bakteriol., 1908, xlv, Part 1, 121.
4. Rivolta: Giorn. di anat. e fisiolog, 1884, x, 10. Quoted by Baumgarten.
5. Johne: Ber. über d. Vet. in Königh. Sachaen für 1884; Dresdon u. f. 1886 and 1887. Quoted by Galli-Valerio.
6. Rabe. Deutsch. Ztschr. f. Tiermed, 1886, xii, 137. Quoted by Galli-Valerio.

experiments made with material obtained from the lesions of the horse. The micrococcus which he obtained formed silvery gray colonies, and these later assumed a yellow tint; an opaque yellow layer developed on potato. Stabbed into gelatin what was regarded as a characteristic change occurred; about the line of inoculation there was feeble liquefaction, a cup-like cavity shaped like a tulip being formed near the surface. All cultures had an odor recalling that of strawberries. No capsule resembling that seen in the tissues was formed in cultures. Inoculation into small animals caused immediate death or formation of an abscess. In the horse, however, a tumor similar to that which occurred spontaneously was produced at the site of inoculation and contained the characteristic capsulated masses of micrococci. Rabe named the microorganism *Micrococcus botryogenes.* Similarly successful inoculation experiments have been performed by Kitt,[7] de Jong[8] and others, but the distinctive cultural characters described by Rabe have not been confirmed.

Kitt regards the organism as a variety of *Staphylococcus pyogenes aureus.* Galli-Valerio,[9] who has studied the cultural characters of an organism obtained from a typical human lesion of the skin containing characteristic masses of cocci, has found no distinctive cultural peculiarities and agrees with the view of Kitt. Poncet and Dor[10] first isolated the organism from a human lesion of the skin and produced on the udder of a she-ass a pedunculated growth which was not examined microscopically; they regard the microorganism as a distinct species. Baumgarten[11] expresses the view that the microorganism is undoubtedly a distinct species belonging to the same group as *Staphylococcus pyogenes aureus,* but regards as distinctive its capacity to form within the tissues a gelatinous membrane about colonies of cocci. This view being accepted, the term botryomyces is not applicable to the microorganism. The name botryocycosis applied to the disease is, like actinomycosis, firmly established in the literature of the subject.

The following case is described because, in the first place, doubt has been expressed concerning the occurrence of botryomycosis in man (see section on pseudobotryomycosis). The case, moreover, is apparently the first recorded instance in which the disease in man has attacked an internal organ, in this instance the liver. Since the disease, it appears, has not been observed in this country, the case may direct attention to

7. Kitt: Centralbl. f. Bakteriol., 1888, iii, 177. Monatsch. f. prakt. Tierheilk.
8. De Jong: Diss. Giessen, 1899. Quoted by Baumgarten 1890, i, 148.
9. Galli-Valerio: Centralbl. f. Bakteriol., 1902, xxxi, Part 1, p. 508.
10. Poncet and Dor: XI congr. français de chirurgie, Paris, 1897; Lyon méd., 1897, No. 43, p. 213 and 1898, No. 5, p. 145; Arch. gen. de méd., 1900, iii, 129, 274. Quoted by Galli-Valerio.
11. Baumgarten: Lehrbuch der pathogenen Mikroorganismen, Leipzig, 1911.

other instances of the same condition. There is no complete record of the autopsy performed on the patient. Unfortunately no cultures were made at the time of autopsy.

CASE REPORT

The patient, a girl aged 11 years, from Sabula, Mo., was admitted to the St. Louis Children's Hospital Aug. 27, 1910, in the service of Dr. George M. Tuttle, who has kindly permitted me to make use of the accompanying history.

History.—The mother of the child is said to have died of tuberculous pneumonia. She has a father and one sister in good health.

In the spring over one year before her admission the patient had scarlet fever and has not been well since that time. She has been losing weight and strength since last November, when she is thought to have had malaria. Her appetite has been poor and at times she has had fever. She has had severe pain in the abdomen and there has been pain at times in the right side, at times in the left.

No horses in the vicinity are known to have been diseased. The patient received milk from a neighboring farm; one cow of the herd showed signs of sickness during the fall and died the following spring "with a wasting disease that affected her water."

Examination.—On admission the patient was a well developed girl but weak and emaciated, having the appearance of a child much older than her real age. The skin was jaundiced and dry and the superficial veins were everywhere much congested. Over the body there was desquamation of the epidermis, and scattered, numerous small ulcers about the size of a pin's head.

The entire epigastric region was distended by what appeared to be a hard, irregular mass continuous with the liver and extending into the left hypochordiac region. The edge of the liver was thin, extended a half finger's breadth below the costal margin in the mammary line and approached to within about a centimeter of the crest of the ilium in the axillary line. There was marked rigidity and tenderness over the entire abdomen, most severe in the epigastric region and in the neighborhood of the left kidney where the pain was so severe that palpation was impossible.

Respiration was rapid, 40 to the minute, and very shallow. With deep respiration there was pain referred to the swelling in the epigastrium. The intercostal spaces, the depressions above and below the clavicle, and the suprasternal notch were much depressed. There was well-marked bulging of both sides of the chest at its base, more marked on the right side. Auscultation and percussion gave no noteworthy information. The apex beat of the heart was displaced to the left and was found just outside the nipple line.

While in the hospital the patient gradually became weaker. Her appetite was fairly good. She passed copious soft white or yellow stools. A stool examined August 31 was grayish-white and contained fat crystals in abundance; there were no bile pigments.

The temperature was invariably between 97 and 98.8 C. save on the second and third days after admission (100) and on the third day before death (100).

The blood examined on August 29 contained 3,272,000 red blood corpuscles, 60 per cent. hemoglobin and 28,400 leukocytes.

The urine while the patient was in the hospital has the following characters: Specific gravity, 1.008 to 1.015; albumin, present; bile pigments, present; sugar, absent; there were granular casts and a few leukocytes.

The patient became unconscious on the morning of September 8, and died with slow, gasping respiration three hours later.

Necropsy.—A necropsy was performed by a hospital intern. A note stated that more than half of the liver substance was involved by a tumor-like lesion which was firm and contained cyst-like cavities filled with pus. Similar abscesses were found elsewhere. There was hydrops of the gall-bladder. Only the liver, which was put in Kaiserling's solution, was preserved.

Liver: On the upper surface of the liver near the posterior border below and on either side of the falciform ligament is a large, irregular, puckered area approxtmately 10 cm. across, where the tissue has a deep yellow color broken by grayish depressed spots. At the margin of this area surrounding it are low rounded

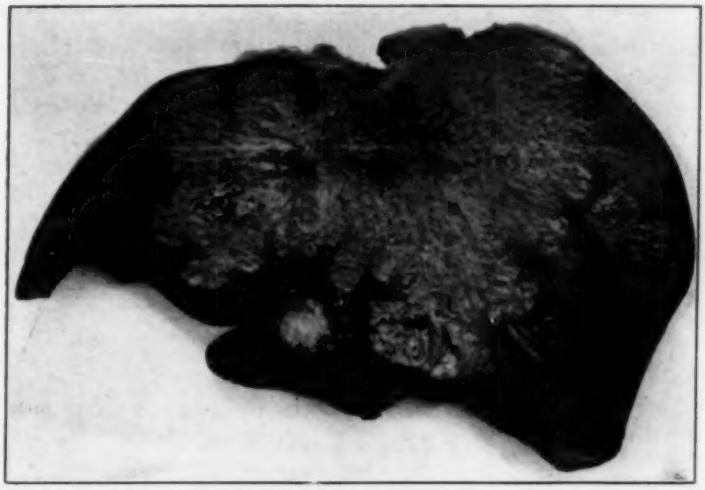

Fig. 1.—Photograph of the cut surface of the liver with botryomycosis. The center of the lesion consists of fibrous tissue; in the periphery are abscess cavities.

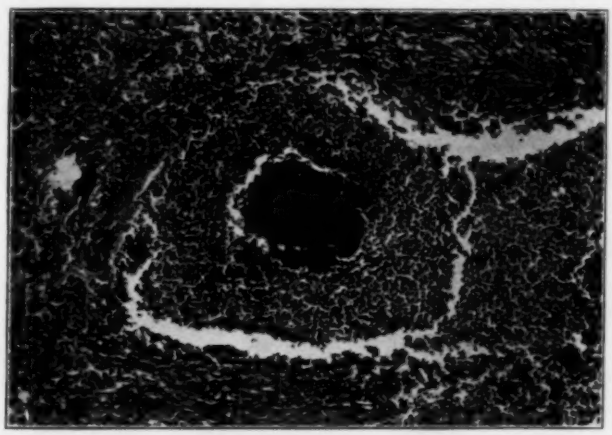

Fig. 2.—Microphotograph showing a botryomycotic granule surrounded by pus and within a cavity the wall of which is formed by newly-formed fibrous tissue.

confluent elevations of the liver substance often 2 or 3 cm. across. The centers of these elevations are soft, have a yellowish tint and correspond to abscess cavities in the underlying tissue. The surface of the liver near these abscesses shows in places bluish-red discoloration. Remains of adhesions are attached to

the surface of the liver at the site of the lesion. Section made transversely through the liver (Fig. 1) shows that an immense tumor-like mass has replaced the greater part of the substance of the organ. The cut surface of the lesion has an irregularly semicircular form with its base corresponding to the upper surface of the liver. Bands of fibrous tissue radiate from the central part of the base which is represented by the irregular puckered area seen on the upper surface of the organ. The tissue composing the lesion varies in different parts. Immediately below the puckered superficial area just mentioned there is a narrow,

Fig. 3.—Drawing showing a botryomycotic granule composed of coccus-like bodies held together by a homogeneous substance which forms a capsule.

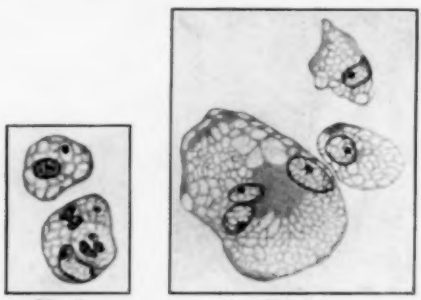

Fig. 4. Fig. 5.

Fig. 4.—Drawing showing phagocytic cells containing droplets of fat.
Fig. 5.—Drawing showing large fat-containing cells which occur in large number within the newly-formed fibrous tissue.

irregular zone of tough, fibrous tissue. The tissue below occupying the center of the lesion is firm and consists of opaque yellow material broken by numerous fibrous bands which in general radiate toward the periphery of the lesion. Further outward the tissue is less dense and there are numerous small cavities filled with soft purulent material. In some places the cavities form irregular, elongated,

communicating channels or sinuses separated by dense fibrous tissue. At its periphery the lesion has a honey-combed appearance and in places there are large abscess cavities. The largest of these cavities is 2 cm. across; it is filled with soft yellowish pus and is lined by yellowish membrane about 0.5 mm. in thickness. On section not more than one-third of the area is represented by normal liver tissue. In this liver tissue lobulation is obscure and there is a greenish tint as if due to jaundice. In the right lobe of the liver outside of the main mass of the lesion are two large portal spaces within which is an elongated channel with opaque yellow wall containing purulent material. Scattered in the remainder of the lobe are minute abscesses collected together in several groups.

The gall-bladder was found at autopsy to be distended, but otherwise showed nothing noteworthy.

Microscopical Examination of Liver.—The liver substance is replaced by masses of dense fibrous tissue in which are cavities containing polynuclear leukocytes and other cells surrounding conspicuous masses of coccus-like bodies (Fig. 2). The fibrous tissue varies considerably, being in places dense and poor in cells, elsewhere loose in texture and richly infiltrated with cells. In this connective tissue occur masses of large cells distended with fat and so abundant that they give to the tissue the yellow color mentioned above. The size of the abscesses and sinuses which contain the colonies of microorganisms varies greatly, and in the older parts of the lesion there are wide channels containing leukocytes and surrounded by fibrous walls rich in cells. There is no abrupt line separating the lesion from the liver tissue which persists. Liver cells at the margin of the lesion are compressed, atrophic and often contain abundant brown yellow pigment. Thickened strands of fibrous tissue separate these cells and in the adjacent relatively normal liver substance fibrous tissue of the portal spaces is considerably thickened.

Botryomycotic granules vary in abundance and size in different parts of the lesion. Three masses, each visible to the naked eye in the stained specimen, the largest being approximately 1 mm. in length, are grouped together in one field of the low power (Obj. 3, Oc. 1). These masses are composed of bodies resembling staphylococci (Fig. 3) which stain deeply with either hematoxylin or methylene-blue. At the edge are the irregular rounded projections which give a mulberry-like form to the entire mass when examined in fresh pus. In some instances the larger bodies in section appear to be separated into several isolated masses. Micrococci appear to be less densely packed together at the center of the mass, which stains less deeply than the outer part. Between the cocci is what appears as a homogeneous background which stains with eosin or picric acid (van Gieson's stain). In many instances particularly about the larger bodies, this homogeneous material is conspicuous at the edge forming a kind of capsule separating the cocci from the leukocytes about. The distinctness with which this clear zone can be made out varies much; in places it may be wholly lacking. The cocci exhibit some variation in size and particularly at the margin of the colony minute microorganisms are found.

Immediately about the botryomycotic granules polynuclear leukocytes occur in large number (Fig. 2). Adherent to the surface of the mass red blood corpuscles are frequently seen. In most instances it is obvious that the botryomyotic granule lies in a small abscess cavity surrounded by pus, for in its immediate neighborhood tissue has disappeared and the purulent exudate (in the hardened tissue) has occasionally retracted from the surrounding wall of fibrous tissue. Leukocytes are usually well preserved, but in places a moderate number have lost their nuclei and are in process of disintegration. Polynuclear leukocytes which have ingested coccus-like bodies similar to those which form the colonies are not infrequent. Scattered cocci are occasionally found outside of cells, but in such instances the leukocytes in the immediate neighborhood are in part necrotic.

The wall of the abscess is formed by fibrous tissue containing numerous cells. In contact with the cavity are large cells with large oval or slightly irregular vesicular nuclei and abundant protoplasm. These cells (macrophages) are phagocytic and contain within their substance red blood corpuscles, nuclear fragments and remains of cells, still recognizable as polynuclear leukocytes (Fig. 4). They occasionally contain cocci similar to those which form the colonies. The regularity and thickness of this zone of mononuclear cells varies greatly. The loose fibrous tissue in the wall of some large abscess cavities is thickly infiltrated over a wide area with cells having the characters just described. Many of these cells are of very large size, four or five times the diameter of a polynuclear leukocyte and distended with the remains of many ingested cells, some of which are still recognizable as polynuclear leukocytes. Similar cells are, in places, vacuolated, vacuoles being formed by fat recognizable by the usual reactions.

In places the connective tissue, perhaps in contact with the zone of phagocytic cells surrounding an abscess, is closely packed with very large cells, whose protoplasm is replaced by vacuoles. These vacuolated cells occurring in the meshes of loose fibrous tissue give it some resemblance to adipose tissue. The nuclei of these cells (Fig. 5) are oval or slightly irregular in outline and situated near the center of the cell. The protoplasm stains faintly, being almost entirely replaced by vacuoles which may be so small that they give the protoplasm a finely granular appearance, or so large that they distend the cell. Occasionally these vacuolated cells are unusually large and have several nuclei, from two to as many as six, collected near the center of the cell. In tissue containing these large vacuolated cells plasma-cells occur scattered in considerable number among them. Sections of the dense yellow tissue (see description of gross appearance) containing masses of the vacuolated cells which have been described, exhibit when stained with Scarlach R. or Sudan III, large red areas occupying a considerable proportion of the tissue. Microscopic examination shows that the cells which by usual methods are vacuolated are filled with fat in large or small droplets; in osmic acid preparations these globules are black. Areas in which the fat-containing cells occur in great abundance are usually in contact with zones containing recognizable macrophages and surrounding foci of suppuration. Transitions from macrophage to vacuolated cells are readily found. The latter appear to be macrophages which have persisted in the meshes of the newly formed fibrous tissue and have undergone advanced fatty degeneration.

In some spots botryomycotic granules are in process of destruction and the surrounding suppuration is in process of disappearance or has completely disappeared. The central coccus-like body may be relatively small; the surrounding tissue may contain no nuclei and appear hyaline. If a cavity persists about the mass of microorganisms polynuclear leukocytes are scant and mononuclear cells have increased at their expense. At a later stage both types of cells have in large part disappeared, the surrounding cavity is absent, and the fixed tissue has approached to the immediate neighborhood of the colony. In contact with the mass of coccus-like bodies is a tissue composed of a fibrillated ground-work and elongated spindle-shaped cells with oval vesicular nuclei. These cells have the characters of so-called epithelioid cells of the tubercle, and in general, directed with their long axes pointing to the central mass, form a zone surrounding the colony. In this zone may occur one or more multinucleated giant cells with many nuclei scattered throughout the cell. Outside of this zone is white fibrous tissue in whose meshes are plasma cells in immense number together with a few lymphoid cells. In some instances a focus or nodule similar to that which has just been described contains no mass of microorganisms in its center and closely reproduces the structure of a tubercle. In the center are one or two large giant cells which have the characters of those seen in tubercles; the nuclei are arranged at the margin of the cell and surround an almost homogeneous area. About the giant cells is a narrow zone formed by a fibrillated

ground-work containing a few cells of epithelioid type. This fibrillated stroma may stain deeply with eosin and exhibit a hyaline appearance. Further outward epithelioid cells are mingled with numerous plasma-cells. Giant cells containing micrococci have been found.

Collections of coccus-like bodies forming large lobulated colonies occur in abundance throughout the lesion. This microorganism acting as an irritant has caused a series of changes in the liver. There is destruction and disappearance of tissue in the immediate neighborhood of the colony and accumulation of polynuclear leukocytes; a cavity containing purulent exudate is formed about the microorganisms. White fibrous connective tissue is formed in abundance in the wall of the abscess. At the margin of the abscess cavity mononuclear cells make their appearance, and acting as phagocytes (macrophages), ingest polynuclear leukocytes, red blood corpuscles and other cells and attain a size many times that of a polynuclear leukocyte. The fibrous tissue nearby is at first rich in cells, containing plasma-cells in immense number. The process of phagocytosis of polynuclear leukocytes and other cells at the margin of the abscess cavity represents an early stage in the process of healing and tends to bring about the disappearance of pus about the parasite. As pus is absorbed the surrounding fixed tissue grows into contact with the mass of microorganisms which are now perhaps killed but not yet dissolved. Cells of epithelioid type and giant cells similar to those of the tubercle come into contact with the persisting microorganism. A lesion resembling, but not identical with, the tubercle is formed. The colony of cocci finally disappears. In the newly formed fibrous tissue between the abscesses there are areas in which large vacuolated cells are so abundant that they form a conspicuous element of the tissue. These cells appear to be mononuclear phagocytes (macrophages) which have persisted in the wall of the abscess and undergone fatty degeneration. They are in places so abundant that they give to the tissue a deep yellow color. Large abscess cavities occur at the advancing margin of the lesion whereas its center is formed by dense fibrous tissue.

HUMAN BOTRYOMYCOSIS

Botryomycosis in man was first described by Poncet and Dor.[10] On the hand of a woman near the digito-palmar fold of the little finger an indolent red spot ulcerated and gave place to a pedunculated tumor the size of a small nut. In sections of the tumor they found the masses of coccus-like bodies to which Bollinger gave the name *Botryomyces,* and by personal observation convinced themselves of the identity of the bodies they observed with those found in the fungus-like growths from the spermatic cord of geldings. Poncet and Dor have perhaps diminished for subsequent observers, the value of these bodies as criteria for the identification of botryomycosis by the interpretation which they have offered. They have maintained the untenable view, wholly unsupported

by the bacteriologists who have studied botryomycosis, that the peculiar bodies are not microorganisms, but products of the degeneration of tissue cells. They regard the coccus-like bodies as pyknotic nuclei. From the lesion Poncet and Dor isolated a staphylococcus, which inoculated into the udder of an ass, produced a small pedunculated growth. No examination of the nodule was made. Poncet and Dor have described as botryomycosis three small pedunculated growths, two being on the hand and one on the most prominent point of the stump formed by amputation of the arm at the shoulder.

Faber and Ten Siethoff[12] have described a group of little nodules on the border of the eyelid occurring at the site of a stye in a boy who had tended a horse suffering with a fungoid growth from the cut spermatic cord. In the viscid pus squeezed from the lesion were mulberry-like masses with the structure of those which occur in the horse. Pedunculated tumors containing similar bodies have been observed in France by Sabrazes and Laubie[13] (in one case on the auricle, in a second on the palm of the hand), and by Delore and Gauthier[14] (in one case above the eyebrow, in a second on the finger). Similar observations have been made in Switzerland; Reverdin and Gulliard[15] have described a pedunculated tumor the size of a pea on the palm of the hand, and Galli-Valerio[9] has seen a nodule of similar size and shape on the anterior surface of the fore-arm.

The disease is apparently much more common in northern Africa than in Europe, and French physicians living in Algeria have described in considerable number instances of a similar but much more severe disease. Brault[16] has described two cases in which small pedunculated tumors containing the characteristically-grouped microorganism have occurred on the fingers of women in Algeria. Legrain[17] has described a considerable number of cases of botryomycosis. Attached to the dorsal surface of the right hand of a Berber woman he found a tumor the size of her fist; it consisted of five masses each pedunculated and the whole attached by a narrow base. A tumor in another Berber woman made its appearance on the stump of a finger accidentally amputated and attained the size of a large mandarin. It was removed, but reappeared, forming a mass larger than before; the growth did not invade the underlying muscles or tendons.

12. Faber and Ten Siethoff: Nederlansche oogheelkandige bijdragen, 1897. Quoted by Bodin.

13. Sabrazes and Laubie: Arch. gèn. de méd., November, 1899; Arch. de parasit., 1898, i, 410.

14. Delore and Gauthier: Gaz. d. hôp., Nov. 8, 1900.

15. Reverdin and Gulliard: Rev. méd. de la Suisse romande, 1900, No. 11, p. 500.

16. Brault: Arch. de parasitol., 1901, iv, 308.

17. Legrain: Arch. de parasitol., 1898, i, 148.

In a subsequent publication, Legrain[18] described other growths on exposed surfaces the largest of which was the size of a child's head. Somewhat similar observations have been made by Archibald[19] on material sent to him from various parts of the Sudan; seven growths removed from the scalp, breast, arm, hand, foot or cheek of natives contained agglomerations of coccus-like microorganisms identical with those peculiar to botryomycosis. The same bodies had been previously observed by a member of the laboratory staff in a growth removed from a camel. In one instance the lesion occurred in a native woman, 45 years of age, who had suffered with a swelling of the breast since childhood; it implicated the entire breast, resembled a fungoid cancer and exuded grayish-white pus from numerous sinuses. In another case a tumor of the scalp implicated the underlying bone and from sinuses on the surface thin pus-containing yellow granules escaped.

Butler and Welsh,[20] in New South Wales, found a swelling outside of the left orbit causing softening of the temporal bone in a child 4 years of age. The scant viscid pus contained numerous yellow granules which consisted of masses of cocci. In a Japanese Kayser and Gryns[21] found the right foot swollen and riddled with sinuses from which escaped exudate containing botryomycotic granules.

PSEUDO-BOTRYOMYCOSIS

Poncet and Dor identified with botryomycosis of the horse the pedunculated fleshy growths in which they found the mulberry-like bodies described by Bollinger. Subsequent writers have given the same name to similar pedunculated nodules, even though they have failed to demonstrate the presence of these readily recognizable bodies. Such growths having the structure of redundant granulation tissue have been described as botryomycosis by Bodin[22] (two cases), Spourgitis[23] (two cases), Gehinet[24] (six cases), Alglave[25] (two cases), Thévenot and Alamartine[26] (five cases), Lenormant[27] (five cases), and others. In none of these cases have botryomycotic colonies been found. To the same growths, Küttner[28] (four cases), who found none of the mulberry-like encapsulated groups of cocci, gave the name *Granuloma telangiectoides*. Two

18. Legrain: Quoted by Gehinet.
19. Archibald: Brit. Med. Jour., 1910, ii, 971.
20. Butler and Welsh: Edinburgh Med. Jour., 1910, iv, 115.
21. Kayser and Gryns: Geneesk. Tijdschr. voor Nederl. Indie., 1907, xiii, Ref. Bull. d. l'inst. Pasteur, 1908, vi, 863.
22. Bodin: Ann. de derm. et de Syph., 1902, iii, 289.
23. Spourgitis: Paris Thesis, 1900. Quoted by Gehinet.
24. Gehinet: Paris Thesis, 1902.
25. Alglave: Bull. Soc. anat. de Paris, 1906, lxxxi, 524, 535.
26. Thévenot and Alamartine: Lyon Chirurg., 1909, ii, 154.
27. Lenormant: Ann. de derm. et de syph., 1910, xi, 193.
28. Küttner: Beitr. z. klin. Chir., 1905, xlvii, 1; Bennecke, München. med. Wchnschr., 1906, 1553.

German writers, Reitmann[29] (one case) and Kreibich[30] (three cases), have adopted the same name for similar growths. Jacquet and Barré,[31] who, like the writers just named, found in their tumors no structures having the characters of so-called botryomyces, think that the use of the name botryomycosis should be discontinued, and the growth they describe should be designated benign hypertrophic granuloma or pseudo-botryomycosis.

Hartzell,[32] describing the same lesion observed in this country (Philadelphia), has suggested *granuloma pyogenicum* to replace botryomycosis of French authors, and this name has been adopted by Sutton,[33] who has described a case which occurred in Liberty, Mo. Wile[34] has described as granuloma pyogenicum two instances of small pedunculated nodules observed in New York City, one on the cheek of a child 8 years of age, the other hanging from the navel of an infant 2 months old. The nodules had the histological structure of granulation tissue, in the first instance richly supplied with blood-vessels. No masses of encapsulated cocci were found within the nodules, but scattered cocci were found at the periphery. Wile describes as typical instances of the same lesion the cases of Hartzell, Küttner, Reitmann, Kreibich and Jacquet and Barré, in none of which were found the characteristic botryomyces of Bollinger, and reaches the conclusion that botryomycosis does not occur in man; he doubts, indeed, the occurrence of a disease, botryomycosis, in the horse, but does not discuss the subject at length.

It is apparent that the diagnosis of botryomycosis has repeatedly been made from the clinical characters of the lesion. A growth makes its appearance usually at the site of an injury on an exposed skin surface, in most instances on the hands or face, and grows rapidly, attaining the size of a small pea or nut. With excessive growth in all directions the mass assumes a mushroom-like or pedunculated form. It is reddish and fleshy in appearance; superficial ulceration occurs frequently and bleeding is readily induced. After partial removal rapid growth occurs. Histological examination shows the usual structure of granulation tissue; young connective tissue is infiltrated with leukocytes and mononuclear cells, and in some instances with plasma cells. In some instances dilated blood-vessels are abundant, but in other instances blood-vessels are not more conspicuous than those in granulation tissue. It is undoubtedly inappropriate to designate this lesion botryomycosis solely because it is fleshy in appearance and pedunculated. In the absence of demon-

29. Reitmann: Arch. f. Derm. u. Syph., 1908, xci, 185.
30. Kreibich: Arch. f. Derm. u. Syph., 1909, xciv, 121.
31. Jacquet and Barré: Ann. de derm. et de syph., 1909, x, 574.
32. Hartzell: Jour. Cutan. Dis., 1904, xxii, 520.
33. Sutton: Am. Jour. Med. Sc., 1911, cxlii, 69.
34. Wile: Jour. Cutan. Dis., 1910, xxviii, 663.

stration of the yellow granules which are peculiar to botryomycosis, the diagnosis is no more possible than the diagnosis of actinomycosis in the absence of the ray fungus. Schridde[35] has recently described protozoa-like bodies within large mononuclear phagocytes found in a pedunculated growth similar to those which have been described. These intracellular bodies are round, oval, semilunar or pear-shape and present some resemblance to the bodies found with kala-azar and oriental sore. No botryomycotic granules were noted in the nodule in which these bodies were found, and he regards the growth as an example of the lesion to which Küttner gave the name granuloma telangiectoides.

BOTRYOMYCOSIS OF HORSES IN THE UNITED STATES

I have been able to obtain no literature on the occurrence and distribution of botryomycosis of horses in the United States. Through the kindness of several veterinary physicians I have received information concerning its occurrence. Dr. V. A. Moore, at the New York State Veterinary College, Ithaca, New York, has seen no instance of the disease. Dr. J. R. Mohler, Chief of the Division of Pathology, United States Bureau of Animal Industry, Washington, has written me as follows: In looking through our card-index catalogue we have failed to find any references to literature on the subject of the occurrence of this disease in this country. Our records of pathological specimens show that Dr. Leon A. Reek of Melbourne, Fla., submitted some tissues from a horse on Nov. 4, 1909, Record No. 3,418, which showed the presence of botryomycosis. This disease in all probability exists in this country, but the cases are not reported.

Dr. Maximilian Herzog has seen several cases in the hospital of the Chicago Veterinary College, but believes that the disease is infrequent in Illinois. Dr. A. T. Kinsley of the Kansas City Veterinary College, writes as follows:

> I have found three cases in horses in Kansas City, two of them involving the spermatic cord, as the sequel of castration. The other involved the point of the shoulder and apparently resulted from infection from a bruise caused by the collar. I have had specimens sent to our laboratory from North and South Dakota, two cases from Nebraska, several from Kansas and one from Iowa in the last five years. In my opinion these cases are not at all rare although I do not know that they are diagnosed commonly, usually being passed over as cases of infection without specific diagnosis.

During four years in Colorado, Dr. B. F. Kaupp saw one instance of botryomycosis, the disease occurring in a mule.

The foregoing data indicate that botryomycosis in horses is uncommon in the states of the Atlantic coast, whereas in the central portion of the United States it is more common. A considerable number of instances have been observed in Kansas City, Mo., a part being from Missouri, a part from neighboring states.

35. Schridde: Deutsch. med. Wchnschr., 1912, xxxviii, 218.

The unusual nature of the lesion which has been described suggests some unusual mode of infection. Botryomycosis of the human skin is not uncommon in certain tropical countries, yet no record has been found of botryomycosis of an internal organ. In the present case the lesion appears to have been primary in the liver and its occurrence here suggests that infection may have occurred by way of the gastro-intestinal tract. There is no evidence in favor of this view save the statement that one cow from which the child received milk at the time of her infection was affected with a fatal wasting disease. Botryomycosis of cattle has been observed, but is uncommon; the disease occasionally attacks the udder.

SUMMARY

Bacteriological examinations indicate that the disease of horses, cattle and swine known as botryomycosis is caused by a microorganism resembling *Staphylococcus pyogenes aureus*, but characterized by the formation of compact colonies held together by a homogeneous material which forms a kind of capsule. About these colonies or granules which are formed only in the tissues there is suppuration and tissue formation producing a lesion which has all the characters of the infectious granulomata.

Human botryomycosis has been observed most frequently in tropical or subtropical countries such as Algeria, the Sudan, Australia and Java. It has been observed in France and Switzerland, but heretofore has not been observed in the United States.

The disease in man affects exposed surfaces such as the hands or face, and has repeatedly followed injuries of infected parts. Pedunculated masses of considerable size may be formed. They consist of newly-formed fibrous tissue in which are foci of suppuration and sinuses opening on the surface. The peculiar botryomycotic granules are always present.

Small pedunculated growths having the structure of exuberant granulation tissue have frequently been described as botryomycosis, although the microorganism peculiar to the disease has not been discovered in the lesion. There is no demonstrable relation between these growths, which have been designated granuloma pyogenicum, telangiectatic granuloma or pseudo-botryomycosis, and botryomycosis as it occurs in man and lower animals.

The case which has been described represents, as far as I have been able to determine, the first instance of the disease described in this country, and is, it seems, the first instance in which it has affected an internal organ. The disease has attacked a child 11 years of age. A massive lesion replaces almost the entire liver and consists of fibrous tissue and foci of suppuration within which occur botryomycotic granules

in large number. It is not improbable that some peculiar mode of infection explains the unusual situation of the lesion. The child received milk from several cows, one of which died with a wasting disease, but no more definite history can be obtained. Botryomycosis has been observed in domestic animals in Missouri where the human instance of the disease occurred.

For the photographs I am indebted to the kindness of Dr. R. H. McBaine. The drawings have been made by Mr. C. D. Jarrett.

1806 Locust Street.

A CASE OF FOREIGN BODY IN THE HEART*

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Numerous cases have been reported in which foreign bodies have been found in the heart at autopsy. In the vast majority of instances entrance to the heart was gained directly through the chest wall. The following case is of especial interest, therefore, as one in which the foreign body reached the heart by way of the venous system, access to the latter having been gained from the digestive tract:

CASE REPORT

History.—D. H., male aged 49, entered St. Luke's Hospital, in the service of Dr. Austin W. Hollis, May 17, 1912, complaining of nausea, fever and muscular pain. Two weeks before entrance, following a spree of five days' duration, the patient had been seized with nausea and vomiting, everything taken by mouth being immediately expelled. The vomitus consisted of food just taken, and the patient had never noticed that it contained either blood or bile. His condition remained much the same for five days, when he began to suffer from fever and pain in the back and legs. He had no headache, nose-bleed or diarrhea. Abdominal pain, urinary disturbance, dyspnea and cough were also absent.

Examination.—On entrance to the hospital, the temperature was 103.6 F., respiration 24 and pulse 100, regular and of good force. Blood-pressure was 140. There was no dyspnea, cyanosis, jaundice, edema or rash. The pupils were equal and regular, and reacted normally. The ears, nose, mouth and throat were negative. The lymph-nodes were not enlarged. There was no rigidity of the neck. Knee-jerks were present and not exaggerated. There was marked tremor of the fingers. The heart apex impulse was neither visible nor palpable. The left border was 11.5 cm. from the midsternal line; the right border was beneath the sternum. The heart sounds were distant but of good quality. There was a short systolic murmur at the apex which was not transmitted. There were no accentuations. Examination of the lungs was negative. The abdomen was somewhat distended and there was slight general tenderness. The liver edge was felt one inch below the free border of the ribs and the edge of spleen could be felt just beneath the costal margin.

A blood culture taken May 18 showed numerous colonies of *Streptococcus viridans* and *Bacillus coli communis.*

On May 18 the white blood-cell count was 22,000, polymorphonuclears 86 per cent., lymphocytes 14 per cent. The Widal reaction was negative. The urine was clear, acid, specific gravity 1.015 and showed a faint trace of albumin. The sediment contained many polymorphonuclear leukocytes and no casts. The stools were not examined for blood, but were never tarry.

On May 20 there were many moist râles and a small area of bronchovesicular respiration and moderate dulness over the right base. The white blood-cell count had risen to 34,000, polymorphonuclears 84 per cent., lymphocytes 16 per cent. The

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* From the Pathological Department of St. Luke's Hospital, New York, F. C. Wood, M.D., Director.

patient ran a markedly irregular temperature varying from 102 to 108 F. He grew gradually worse and died May 21.

Necropsy.—Autopsy was performed six hours post mortem. The body showed no marks of external violence, no edema or jaundice, and no ecchymoses of the conjunctiva or elsewhere. The peritoneum was normal and contained no fluid. The dome of the diaphragm was on a level with the fifth rib on either side. The liver edge was at the costal margin. There were 300 c.c. of slightly cloudy yellow fluid in each pleural sac. The apices of both lungs were bound by old fibrous adhesions and there were small scattered areas of bronchopneumonia in the right lower and left upper lobes. The pericardium contained 75 c.c. of unclotted blood. Protruding 1.5 cm. from the posterior tip of the right auricle was the end of an ordinary wooden toothpick which measured 6.8 cm. in length. The other end could be felt within the auricle, pressing against its anterior wall at the right auricular appendage. Over this end the wall was thinned, white and covered with fibrin over a small area about 3 mm. in diameter. The toothpick was held in place within the auricle by a soft "chicken fat" clot. At the upper part of the pericardium posteriorly there was an area, 1 cm. in diameter, which was abraded, but not pierced, by contact with the end of the toothpick. Adherent to the surface of the pericardium were several small plaques and shreds of fibrin. Numerous small ecchymoses, from pin-point to 1 mm. in size, were present on the epicardium, especially numerous over the upper posterior part of the left ventricle. The heart was preserved in gross without sectioning.

The pharynx, larynx, trachea, esophagus and stomach were all normal. On the posterior wall of the duodenum, 14 cm. beyond the pylorus, at the lower part of the descending portion where it lay directly over the inferior vena cava, was a small ulcerated area, about 5 mm. in diameter. Extending backward and upward from the base of this ulceration was a sinus, 1.5 cm. in length, which easily admitted a probe 2 mm. in diameter, leading directly into the inferior vena cava. The intestine was otherwise normal. The intestinal contents were of normal brown color.

In the anterior wall of the inferior vena cava, 8 cm. below the entrance of the hepatic vein was the opening of the sinus from the duodenum previously described. Surrounding this opening the wall over an area 5.5 cm. lengthwise of the vessel and 2.5 cm. transversely, showed a rough, eroded surface covered with a small amount of loose fibrin of a greenish color, suggesting bile staining. A small fibrinous clot adherent to the edge of the sinus had evidently plugged it before death.

The other organs, except for a large soft spleen weighing 360 gm., showed nothing of particular interest either grossly or on microscopic examination.

OTHER REPORTED CASES

Nineteen cases have been reported in the literature in which foreign bodies have been found in the heart at autopsy, omitting the large number in which entrance to the heart was gained directly through the chest wall. The articles found were needles, pins, fish-bones, teeth, a thorn, etc. In one of these nineteen cases a needle had pierced the bronchus, pericardium and heart. In a second case the patient had swallowed two false teeth on a gold plate. The gold plate had pierced the esophagus and pericardium, the patient dying of a purulent pericarditis. In a third case, a fish-bone had pierced the stomach wall, near the esophageal opening, and subsequently the diaphragm, pericardium and heart, the sharp

end of the bone having been found protruding into the heart and the blunt end into the stomach. In two cases there was a definite history of swallowing the foreign body which was found in the heart, but no lesion of the digestive tract and no indication of the route followed were found. These two cases are of interest on account of the length of time during which the foreign bodies had in all probability been present in the heart and the slight or entire lack of heart symptoms due to their presence. In one, a case reported by Ambrose, a pin, which had been swallowed nine years previously, was found in the wall of the right ventricle. The patient died of perforated gastric ulcer without having had heart symptoms in the interval. In the second case, reported by Kussmaul, a thorn of *Prunus spinosa*, covered by a thick layer of fibrin, was found free in the cavity of the right ventricle. The spine had been swallowed one and a half years previously, and following this the patient had been troubled for some time with precordial pain. He died of pulmonary tuberculosis.

In the remaining fourteen cases no indication of the place of entrance was found and no definite history was obtained. In twelve of these the foreign body was believed to have been swallowed, and may have been in all. In several, however, it was a question whether the foreign body might not have been inserted through the skin. In four of the cases, the writers believed, but without proof, that entrance to the heart was obtained directly through the esophagus and mediastinal tissues.

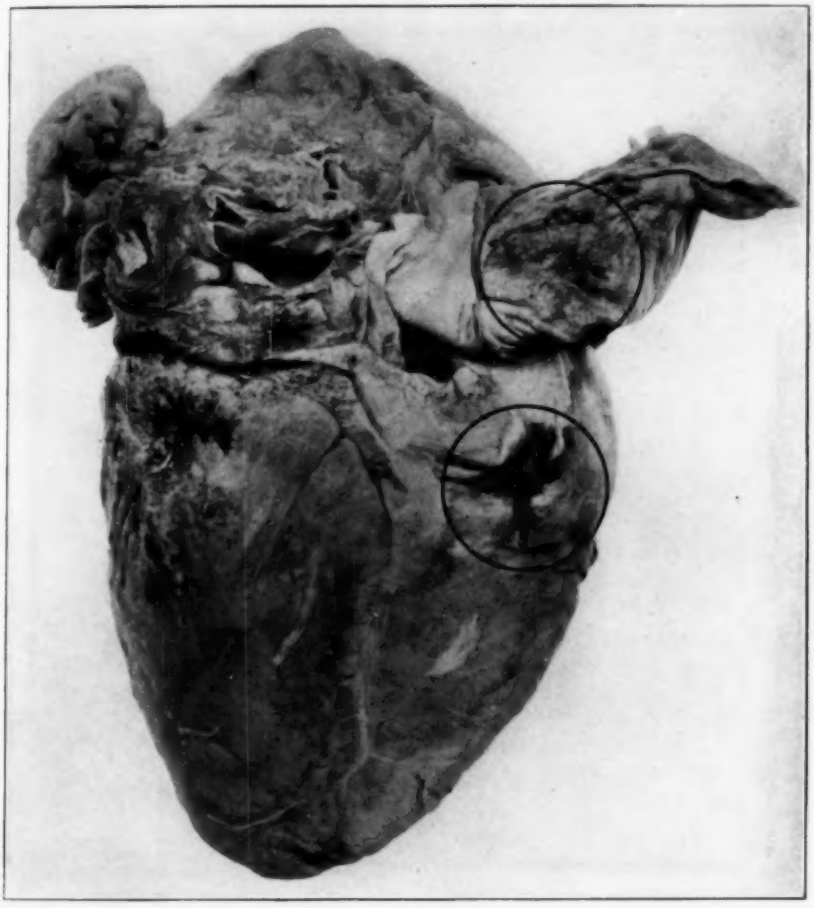
A case reported by Benda, not included in the above series, is also of interest. In this a fish-bone was found in the superior mesenteric vein, but no lesion of the digestive tract was discovered.

DISCUSSION

The case here reported seems then to be unique in that the foreign body was proved to have reached the heart by way of the blood-stream, its point of entrance into the latter from the intestine having been demonstrated. It is probable that this occurred in some of the cases quoted above, and its possibility is discussed at considerable length in the literature. Oppel, working with rabbits, was unable to demonstrate that needles could travel in the blood-stream, and doubts whether this ever occurs in man. Haecker, from experiments on dogs, arrived at a similar conclusion.

The route traveled by the toothpick in the case reported was a short one. A smaller object, however, which could easily have passed the tricuspid and pulmonary orifices, would have been carried on to the lungs, and one small enough to pass easily through vessels of small caliber might have traveled a much greater distance to the heart. A wooden object

would naturally be more easily carried along by the blood-stream than a metal one, especially if the latter were sharp-pointed, as a needle or pin. There seems, however, little room for doubt that many of the foreign



The lower circle surrounds the end of the toothpick which protrudes from the posterior tip of the right auricle. The upper circle surrounds the surface of the pericardium at the point where it has been roughened by contact with the protruding end of the toothpick.

bodies, as fish-bones and even pins and needles, which have been found in the heart reached it by way of the blood-stream, as did the toothpick in this case.

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A STUDY OF RESPIRATION AND CIRCULATION IN EPILEPSY *

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Modern methods of study have already assisted in the explanation of many of the physiological facts bearing on circulation and respiration, and have explained the pathogenesis of many of the disorders of these systems.

An analysis of the clinical features of epilepsy reveals a vague and unsatisfactory description of the symptoms referable to the circulatory and respiratory systems.

A study of some of the circulatory and respiratory disturbances of epilepsy by modern methods of investigation was therefore considered important.

This report is based on the results obtained from the examination of forty-four cases. All of these cases were examined on two, some three and four and a few up to fifteen different occasions.

The examination included a graphic study of the heart action, employing tracings of the jugular and brachial pulses and the apex beat. Blood-pressure estimations and continuous blood-pressure and respiratory curves were made. There were 225 tracings obtained from the forty-four patients.

The tracings were obtained by means of the Erlanger sphygmomanometer with a Hirschfelder attachment, and an Ellis pneumograph.

This report is not as extensive as we could wish, nor the evidence as voluminous as it should be. The difficulty of obtaining a continuous blood-pressure curve on a patient during a convulsion is self-evident. The obtaining of a tracing which includes the time preceding and following the convulsion is largely a matter of luck and many tracings may be made before one is successful.

The association of epilepsy with heart disease has been observed for many years. This association may be the result of several factors. First, the heart disease may be accidental. Second, the epilepsy may be responsible for the cardiac changes, and, third, the cardiovascular change may be responsible for the epilepsy. The third group is a small one and

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includes the late or tardy epilepsies. This condition having no bearing on our findings, will not be discussed. It is, however, fitting to call attention to the so-called epileptic convulsions accompanied by stoppage of the heart, bradycardia or other arhythmia.

Bradycardia has been noted by Seguin (21-24) Corkey and Hubberty (11-76), Drummond (5-15), Gibbings (12) and many others. In the light of our present knowledge of heart-block it is extremely probable that it was this condition which the above authorities observed.

Stoppage of the heart (?) has been observed by Moxon and Tagge and Smith while auscultating the heart. Failure of the pulse has been observed by Hughlings Jackson and Russel. Whether these cases were heart-block or hemisystole cannot be said, for lack of graphic records. Munson[1] did not find a single case of stoppage of the heart in epilepsy, employing graphic methods as a means of study.

There are found in the literature numerous references to the abnormal condition of the heart in epilepsy. Valvular lesions, hypertrophy and arhythmias have been frequently noted.

Browning,[2] after examining 150 cases, states that normal sounds and a normally acting heart are the exception rather than the rule.

Of the forty-four cases examined by us, thirty-five showed an abnormal condition of the heart; of these, ten showed gross lesions and twenty-five a functional change manifested by hemic murmurs, abnormality of sound and sinus arhythmia. Valvular lesions were observed four times. Hypertrophy was observed seven times. Diastolic irregularity was observed twelve times. Abnormal sounds were observed thirteen times. Hemic murmurs were observed four times. Heart block was observed once. Irritable heart was observed once. Nodal rhythm was observed once. Auricular extrasystoles were observed once. The case of heart-block exhibited true epilepsy and not the syncopal attacks of the Stokes-Adams syndrome. Although it is generally agreed that sinus arhythmia is of vagal origin, no relation between it and the Traube-Hering waves (to be described later) was observed. Hypertrophy of the heart occurred in patients in middle life or above, with two exceptions.

BLOOD-PRESSURE

Owing to the diversity of methods employed by the numerous investigators, and the mechanical defects of many of their instruments, the work of the older authors, such as Feré, must be discounted. Of the more recent investigations it may likewise be said that the methods differ, that the observations have been too limited in number, and that graphic methods allowing of the study of continuous blood-pressure

1. Munson: Jour. Am. Med. Assn., 1908, l, 681.
2. Browning, Wm.: Jour. Nerv. and Ment. Dis., 1893, xviii.

curves have not been utilized. It is apparent that one cannot detect a change in blood-pressure occurring within the space of several seconds by the use of such instruments as the Riva-Rocci, Janeway, Stanton, etc.

Summed up, the results of the more recent investigations are as follows: There is a high blood-pressure during the convulsion; the blood-pressure falls rapidly after the convulsion, but remains higher than normal between convulsions. (Plaskuda, Morgenthaler, Fleury, L'Allemant and Rodiet and others.)

Our results will be tabulated under the following headings. 1. General blood-pressure. 2. Respiratory change in blood-pressure. 3. Traube-Hering waves. 4. Changes relative to the convulsion.

1. Of 41 cases examined as to general blood-pressure, 18 had a systolic blood-pressure of 120 or below, and 23 above 125 ranging to 200. Of 17 cases examined on the day of a convulsion, seven had a systolic blood-pressure above 135, and 10 were below 120.

The pulse-pressure, estimated by the difference between the systolic and diastolic pressures, was 50 or above in 21 cases, 40 or above in 15 cases and 45 in 5 cases. Of 8 cases showing a pulse-pressure above 55, 5 were either measured on the day of a convulsion or had some cardiovascular disease.

Owing to the paucity of material, and taking into consideration the individual variations, variations of emotion, sensory stimuli, etc., no hard and fast conclusions can be made from this particular part of the work. The systolic blood-pressure and pulse-pressure were higher than normal in a little more than one-half the cases; the pulse-pressure was below normal in many. The cases showing cardiovascular disease had high pulse-pressure. The cases showing high systolic blood-pressure on the day of a convulsion likewise showed a high pulse-pressure.

2. Respiratory change in blood-pressure: In 21 cases showing respiratory changes in blood-pressure our results bear out Erlanger and Festerling's[3] findings. The arterial pressure falls during inspiration and rises during expiration. During the labored breathing following a convulsion, the respiratory changes in blood-pressure are very marked.

3. Traube-Hering waves: Under certain unusual conditions, there are found in addition to the respiratory rhythmical falls and rises of blood-pressure, changes in blood-pressure, the waves of which are much larger than those due to respiratory movements. These waves were first described by Traube.[4] Hering[5] considered them as arising as a result of irradiation from the respiratory center. Horatio Wood, Jr.,[6] in a

3. Erlanger, Joseph, and Festerling, E. G.: Jour. Exper. Med., 1912, xv, No. 4, p. 37.

4. Traube: Centralbl. f. d. Med. Wissensch., 1865, p. 1881.

5. Hering: Quoted by Horatio Wood, Jr. (see note 6).

6. Wood, Horatio, Jr.: Am. Jour. Physiol., 1899, No. 2, p. 352.

study on the origin of Traube waves, comes to the conclusion that they do not arise in the respiratory center. He was able to paralyze the respiratory center through the action of veratrin, the vasomotor center remaining intact. Under these conditions he was still able to observe Traube waves (Fig. 1).

The ultimate cause of these waves is not well understood, but they are probably due to a rhythmical activity of the vasomotor center. Although a rhythmical activity of the vasoconstrictor center is said to be present throughout life, there are no definite data relative to the occurrence of these waves in man.

They have often been observed during experiments on animals, especially in experiments increasing the intracranial tension. They have likewise, occasionally, been observed in apparently normal human subjects. However, although present at times, they are the exception rather

Fig. 1.—Traube-Hering waves not due to respiratory change. Upper tracing, respiration; lower, blood-pressure.

than the rule. Many other waves of change in blood-pressure may be observed in man and should be definitely differentiated from the Traube-Hering waves. Emotion, muscular movement, peripheral stimulation, etc., all produce change in the continuous blood-pressure tracings. Changes due to muscular movements can easily be differentiated, as pointed out by Erlanger;[3] those due to emotion, etc., are not rhythmical and do not have a gradually increasing and diminishing size. In the interpretations of our tracings the following conditions were insisted on before Traube-Hering waves were said to be present. 1. The column of mercury in the manometer had sunk to its lowest level after inflating the arm-band before the drum was started. 2. All muscular movements were carefully watched for, and marked as such on the drum. 3. All waves due to emotion and other causes were excluded. 4. Following the convulsion the column of mercury was at the same level as before it. The

waves will be described relative to their occurrence, length and relation to pulse change.

Of the 44 cases, 24 showed the presence of Traube-Hering waves. Of 15 cases examined on the same day as the convulsion, 7 showed marked waves, 6 moderate waves and 2 no waves.

Of 14 cases examined within five days after a convulsion, 3 showed marked waves, in 7 waves were present and 4 showed no waves.

Of 15 cases examined more than five days after, one showed moderate waves twenty days from a convulsion. It was observed in those examined immediately preceding and following a convulsion that the waves were more marked at this time.

Of the 24 cases showing waves, 13 were present in cases showing a definite aura, 4 in those showing no aura and 7 in whom a history could

Fig. 2.—Relatively low blood-pressure during petit mal attack

not be obtained. Four other cases showing an aura had no waves. The tracings on these cases were not taken on the day of a convulsion and none of them had a pneumogastric aura.

The duration of the waves ranged from 13⅓ to 35 seconds. The greater number ranged from 13⅓ to 26 seconds. The duration of the waves remained constant in each individual, and the series may be divided into three groups possessing waves 13.33 to 18.66, 20 to 22 and 24 to 28 seconds.

Of 39 cases the pulse-rate was slower during the high blood-pressure, in 17 cases, more rapid in 3, and unchanged in 18. It is safe to say that when the pulse changes in rate, it is usually slower during the period of high blood-pressure.

4. Pulse and blood-pressure in relation to the convulsion: It would be useless to give a review of the literature on these points for the reasons

outlined above. Most authors agree that there is an increase of blood-pressure preceding and during the convulsion, that it rapidly falls after the convulsion, but remains higher than normal throughout. The pulse-rate is said by most observers to be increased during the convulsion. Some state that it is slow; it is possible that these cases may be the bradycardias of heart block. Morganthaler goes further and states that the blood-pressure is labile after the convulsion.

We have obtained tracings showing continuous pulse- and blood-pressure curves before, during and after the convulsions, on three dif-

Fig. 3.—Alternating type of respiration following a petit mal attack.

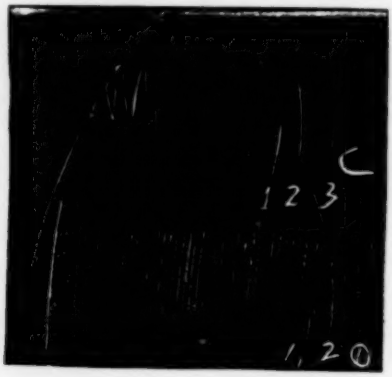

Fig. 4.—Petit mal attack. 1. Drop in blood-pressure. 2. Apnea. 3. Convulsion.

ferent patients, and on one during and after the convulsion. In one case we have obtained eight tracings, showing seven petit mal and one grand mal attack each. In another case two grand mal attacks and in two cases one grand mal attack each. In all of these cases there was seen in addition to the Traube-Hering waves, (1) a preliminary rise in blood-pressure occurring from twenty-six to sixty seconds before the convulsion. Where the rise occurred over thirty seconds before a convulsion the blood-pressure usually fell again slightly; (2) immediately preceding the con-

vulsion by from nine to twelve seconds and in one case twenty-eight seconds (this was a case of grand mal attack) there was a sudden marked drop in blood-pressure lasting from eight to thirteen seconds (Fig. 2). The pulse in every instance became rapid and remained so during the convulsion and for a short time following it. The increase in rapidity of the pulse occurred at the time of drop in blood-pressure. The blood-pressure remained relatively low during the time occupied by the petit mal attacks in all fits, and rose within five seconds after the attack. The blood-pressure rose rapidly and markedly, in many instances showing rhythmical variations, and then gradually subsided to the normal level.

In the grand mal attacks we are unable to state positively whether the relatively low blood-pressure persists throughout the entire attack, because of the interference by arm movements and the consequent late appearance of a regular blood-pressure curve. In one of these tracings it can plainly be seen that the blood-pressure is low for a considerable time during the convulsion. It must be said, however, that in tracings taken during the grand mal attacks the blood-pressure is high at cessation of the attack. In one attack of petit mal type in which we were able to note the beginning of the aura, it was found to follow the drop in blood-pressure by two and two-thirds seconds and to precede the apnea by two seconds.

RESPIRATION

The respiration will be studied from two standpoints: 1. Rhythmical change in type of respiration. 2. The respiration in relation to the convulsion.

In twelve of the forty-four cases of rhythmical change from rapid, regular and shallow, to slow, irregular and deep was noted within a short period preceding and following a convulsion. Eleven of these cases showed well-marked Traube-Hering waves of blood-pressure. The changes in respiration did not have any definite relation to the changes in blood-pressure indicated by the Traube-Hering waves, nor to the bloo -pressure in general. A change similar to this has been noted in meningitis by Conner[7] (Fig. 3).

In five cases one or more periods of apnea were observed lasting from sixteen to thirty seconds. During this period there was seen a fall in blood-pressure and in one case two rhythmical waves of change in blood-pressure. This apnea occurred at times having no bearing on the convulsion.

A study of the respiratory change in relation to the convulsion was possible in five tracings taken during petit mal and three tracings during grand mal fits in three different patients. In every example of petit mal attacks in one patient it was seen that there was a cessation of respiration preceding the convulsion by four to twenty-six seconds, more often four

to nine seconds. The apnea persisted throughout the convulsion and lasted from thirteen to sixty seconds. It was interrupted in a few instances by several deep and irregular respirations. The apnea commenced at the height of inspiration. It was in every instance preceded by the fall in blood-pressure by from two and two-thirds to six and two-thirds seconds.

In the tracings of the three grand mal attacks, in each instance the fall in blood-pressure preceded the apnea, and the apnea preceded the convulsion as in the case with petit mal attacks. We are unable to state definitely how long the period of apnea lasted relative to the convulsion in these cases. The tracings show either an apnea or an apnea interrupted by slow and irregular respiratory movements.

Before taking up the discussion of the relation of our findings to the various theories of the pathogenesis of epilepsy, we shall make a résumé of those conditions which may have a bearing on a causal relation to epilepsy.

There were present a number of diastolic arythmias considered to be of vagal origin. A large number of cases showed Traube-Hering waves, especially those cases having an aura. These waves were particularly prominent during the time near or following a convulsion, and practically disappeared after five days.

Rhythmical respiratory movements were found in a considerable number of cases, with one exception always associated with, but having no relation to, the Traube-Hering waves.

The convulsions showed a sequence of events as follows: A preliminary rise in blood-pressure followed by a sudden fall, than an aura, then a period of apnea and then the convulsion. The blood-pressure remains relatively low throughout the petit mal and also probably throughout the grand mal attacks. The pulse becomes rapid with the fall in blood-pressure and remains so during the convulsion (Fig. 4).

The literature on the pathogenesis of epilepsy is especially rich. The theories are numerous and contradictory and the evidence is inconclusive. We shall content ourselves with mentioning some of the theories, first, as to the stimulus that determines the discharge, and second, as to the seat of discharge.

Relative to the nature of the stimulus we shall confine ourselves to the question of anemia and hyperemia of the brain. Anemia of the brain as the cause of unconsciousness and convulsion has been supported by Kussmaul and Tenner, Nothnagel, Riegel and Jolly, Gutnikow and many others. The gap between the several steps of reasoning employed by these authors is considerable.

The facts that anemia of the brain can produce convulsions and that

7. Conner, Lewis A.: THE ARCHIVES INT. MED., 1912, ix, 203.

a pallor of the face has been observed by these authors during the attack, is certainly insufficient evidence to establish anemia as the cause of unconsciousness or convulsions.

On the other hand, hyperemia of the brain has likewise been supported by many, Landois, etc. Recently it has been found that, during experimentally produced epilepsy, hyperemia and not anemia of the brain is present during the convulsion. (Rabinowitch, Berger.) We shall refer to these observations again.

As to the seat of discharge, we have a great number of observers arrayed against one another, one group assuming the medulla and pons to be the site of discharge, Nothnagel, Van d'Kolk, Reynolds, Echeverria, Kussmaul, etc., the other placing it in the cerebral cortex — Charcot, Ferrier, Luciani, Gowers, etc. — while Hughlings Jackson suggests that fits might result from discharge of lesions in either of these two.

It is not necessary to enter into a detailed account of the experimental work tending to prove either of these theories. Suffice it to say that convulsions may be caused experimentally through irritation of either of these regions.

The experimental production of convulsions by irritation of the cortex and the occurrence of convulsions as the result of disease of the cortex has led to the conclusion, as yet unproven, that the greatest number of convulsions originate in the cortex. This does not exclude the medulla and pons as the site of discharge in some convulsions.

J. Hughlings Jackson and H. Douglas Singer[8] suggest that in addition to the cortical type of epileptic fits, there occur, in the human subject, bulbo-pontine (lowest level) fits, analogous to those experimentally produced in some lower animals. They offer in support of this hypothesis a case showing fits which definitely began by convulsions of the respiratory muscles. Of special interest is the observation that with the beginning of the earliest motion of the convulsion, respiration ceased and was not resumed until the end of the fit, which lasted from forty to sixty seconds.

Harvey Cushing[9] has contributed some very important data as to the relation between increased intracranial tension, cerebral anemia and respiration. He has found that at a stage during the height of compression there occur Traube-Hering waves, and Cheyne-Stokes respiration associated with rhythmical change in blood-pressure, the low blood-pressure corresponding to the period of apnea. It would seem that the period of apnea is the result of cerebral anemia produced by the increased intracranial tension and the relatively lower general blood-pressure.

8. Jackson, J. Hughlings, and Singer, H. Douglas: Brain, 1902, xxv, 122.

9. Cushing, Harvey: Am. Jour. Med. Sc., 1902, cxxiv, 375; 1903, cxxv, 1017; Bull. Johns Hopkins Hosp., 1901, xii, 290.

It can readily be seen that all experiments on the cerebral circulation must take into consideration intracranial tension, and such experiments as include the opening of the cranial cavity without subsequently closing it, must be discarded.

The fact that increased cerebrospinal pressure has been observed during the convulsion of epilepsy (Bianchi,[10] D'Ormea), adds considerable speculative interest to our observations that there is present an undulatory respiration and Traube-Hering waves together with a fall in general blood-pressure preceding the convulsion in all our cases.

It would be important to determine by further work any possible relation between the changes found by us and any change in the cerebrospinal pressure, perhaps similar to the changes found by Cushing in experimentally producing increased cerebrospinal pressure. From our experiments no definite conclusions can be made as to the state of the cerebral circulation at the time of convulsion, inasmuch as the intracranial tension was not measured. A vasoconstriction of the peripheral vessels does not necessarily indicate a similar condition of the cerebral vessels.

Our one case in which petit mal attacks were studied is very similar to the case described by J. Hughlings Jackson and H. Douglas Singer and shows definitely that, whatever the nature of the stimulus, the site of discharge either acts on both the cerebrum and medulla and pons, or on the medulla and pons alone.

The presence of unrest of the vasoconstrictor and respiratory centers shown by the Traube-Hering waves and undulatory respiration, the fall in blood-pressure preceding the convulsion, and the cessation of respiration probably due to vagal interference, as well as the aura of pneumogastric type following shortly after the fall in blood-pressure, all point to the bulbopontine region as a site of disturbance.

The irritation may have commenced at the cortex and spread downward, being felt in the medulla first, or it may have commenced in the medulla and spread upward; in this particular type of case we are of the opinion that the site of discharge is in the medulla. We are unable to say if the same is true of grand mal attacks and obviously cannot make any assertions for epileptic convulsions in general. It is noteworthy that the sequence of events in the petit mal attacks of one patient was the same as that observed in a grand mal attack in the same patient and that two other grand mal attacks in two other individuals presenting a clinical picture of ordinary epileptic convulsions likewise showed similar manifestations.

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10. Bianchi: Ann. di. Neurol., 1911, xxix, Part 3.

CONCLUSIONS

It may be stated that with regard to the cases observed by us:

1. There are present in many cases of epilepsy rhythmical variations of blood-pressure other than those due to respiratory movements.

2. The sequence of events relative to a convulsion is as follows: A preliminary rise in blood-pressure followed in series by a sudden drop of blood-pressure, a period of apnea, and then the convulsion.

3. The blood-pressure was relatively low during convulsions of petit mal type and during some of the corresponding period of the fits of the grand mal type.

4. The pulse was rapid during the convulsions.

5. A study of the changes in the respiratory and circulatory systems in some of the cases of epilepsy suggests that the site of discharge is in the medulla and pons (the "lowest level of fits" of Hughlings Jackson). Likewise it points to the medulla as participating in the discharge in all cases of epilepsy whether this discharge originates there or not.

We wish here to express our gratitude to Dr. H. Douglas Singer, director of the Institute, for his encouragement and kind assistance.

A MODIFICATION OF RUSSO'S URINARY TYPHOID FEVER TEST, WITH A REPORT OF ITS USE IN ONE THOUSAND CASES, AND A COMPLETE BIBLIOGRAPHY *

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As a preface to the discussion of the urinary methylene-blue test for typhoid fever, it seems best to point out a few facts regarding the value of blood-cultures in the diagnosis of typhoid fever. By the use of the more modern methods for the isolation of the typhoid bacilli from the blood, the blood-culture has been so uniformly successful that it is now recognized as the diagnostic means, *par excellence,* especially for an early diagnosis. This procedure is, of course, to be recommended in all cases, but the average practitioner does not possess the necessary laboratory skill or apparatus for this test, the technic being rather difficult. It is for this reason that a number of tests which might be classed as secondary or corroborative are of much clinical value and significance, each one strengthening the physician's diagnostic armamentarium. The urinary methylene-blue test is placed in this class of corroborative tests, and is discussed with that view-point in mind.

THE RUSSO REACTION

The use of methylene-blue in the urine as an aid in the diagnosis of typhoid fever was first described by Russo[1] in 1905. The technic, as described by Russo, was as follows. To 4 or 5 c.c. of the patient's urine add 4 drops of a 0.1 per cent. aqueous solution of methylene-blue. After thoroughly mixing, examine against the light. A positive reaction is indicated by an emerald or mint green. Any tinge of blue renders the reaction negative. This reaction, according to Russo, is not affected by boiling, nor by the ingestion of such drugs as calomel, quinin, salol and caffein. If the urine is examined from day to day, a returning bluish tinge denotes the beginning of convalescene, and is regarded by Russo as a favorable prognostic sign. He obtained positive reactions in urines in which the specific gravity was from 1.016 to 1.030. The reaction was constantly negative in normal individuals, both young and old, and in pregnancy, labor, scarlet fever, chicken-pox, small-pox, influenza, acute and chronic bronchitis, lobar pneumonia, bronchopneumonia, acute and

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* From the Laboratory of Georgetown University Hospital.

1. Russo, M.: La bleumetilene-reazione, suo valore clinico. Riforma med., Palermo-Napoli, 1905, xxi, 507.

chronic gastric catarrh, gastroenteric fevers, appendicitis, renal calculus, abscess of the liver, articular rheumatism, mitral insufficiency, epilepsy, neurasthenia and malaria. A positive reaction was also present in measles and in some severe cases of tuberculosis. In the latter, the appearance of a positive reaction did not denote the height of the fever, but indicated the severity of the infection. The reaction has no relation to indican and is probably caused by toxins excreted by the kidney. Privisteria later corroborated the work of Russo.

The subsequent work with the urinary methylene-blue reaction has not been particularly extensive, and does not tend to confirm the conclusions of Russo.

Cousin and Costa,[2] using the method as described by Russo, obtained a positive reaction in any urine which was dark, that is, concentrated. This obtained not alone in typhoid fever, but in any other disease in which the urine was dark. By diluting a concentrated urine which had given a positive reaction, a blue or negative reaction was obtained, and by concentrating a pale urine which had shown a negative reaction, a green or positive reaction appeared. They concluded that the production of an emerald or mint green was not a chemical, but a physical phenomenon; in fact, that it was a metachromasia, produced by the yellow of the urine plus the blue of the reagent. They also used the method of Roch, and Boudin and Monchton, by suspending a tube of the blue solution in a large tube of the yellow urine, when a green was produced in the lower portion of the tube. Russo's facts are not disputed, but his interpretations of them are. Their final conclusion is that it is of no diagnostic value, since in any febrile condition the urine is concentrated in the early stages, and gradually becomes lighter in the stage of convalescence. The above conclusions were confirmed by Gandy,[3] Lesieur,[4] Theodoroff,[5] Spieshoff,[6] Frankel, Dmitrenko,[7] Dunger,[8] Dibailoff[9] and Iovanne.[10]

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9. Dibailoff, S. J.: Diagnostic Value of Russo's Reaction. Vrach. Gaz., St. Petersburg, 1909, xvi, 5.

10. Iovanne, A.: La bleumetilenereazione nelle urine dei bambini sani ed ammalate. Pediatria, Napoli, 1906, iv, 267.

Landolfi[11] agrees with the above authors that the reaction is simply a physical phenomenon. He examined particularly cases of tuberculosis, and whenever the color produced was green or greenish blue, using the method of Russo, he repeated the test after decolorization. The urine was decolorized by first correcting the reaction if alkaline, boiling and filtering to remove the albumin. To 10 c.c. of the filtrate from 5 to 10 drops of a saturated solution of lead acetate was added, and then filtered through a double filter. With 5 c.c. of this filtrate the test was made in the usual manner. In a few cases of tuberculosis in the last stage, a positive reaction was still obtained. Working on the basis that a small amount of indican is normally present, a deep green produced with a small amount of indican is considered positive, while a greenish-blue with a large amount of indican is considered negative. He, however, does not regard it as of diagnostic value.

Carletti[12] confirmed the work of Landolfi, and quoted Monchton as believing that the green reaction was due to bilirubin. However, the reaction is present even in urines showing no bile with ammoniated zinc. He stated that the specific gravity and reaction of the urine had no effect, and that the coloration disappeared in from twelve to twenty-four hours, leaving the granules of pigment floating on top, although Russo claims that the color lasts about ten days. Carletti considers these as strong arguments in favor of the hypothesis of a physical phenomenon.

Grossi[13] followed the decolorization method of Landolfi and confirmed his results, showing a few positive results even after being decolorized. However, Grossi, claiming that the decolorization was not complete, added a larger quantity of lead acetate and afterwards used animal charcoal to insure a thorough removal of all coloring matter. Using this method, a positive reaction was never obtained in a large series of various diseases, in which a positive reaction was obtained before decolorization, in all cases, and in a number when using the method of Landolfi.

The results of the researches of Landolfi, Grossi and Carletti were confirmed by Montefusco,[14] Tolane and Ferrari.[15] The latter also had similar results by decolorization with charcoal alone, as he believed that the other method might cause some chemical changes. An examination of the urine before and after decolorization, showed some slight changes.

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11. Landolfi, M.: La Bleumetilenereazione. Riv. crit. di clin. med. Firenze, 1906, vii, 705.
12. Carletti, M.: Interno alla cosi detta bleumetilenreazione. Gazz. d. osp., Milano, 1906, xxvii, 146.
13. Grossi, T.: Ancora sulla cosidetta bleumetilenereazione. Gior. internaz. d. sc. med. Napoli, n. s., 1907, xxix, 268.
14. Montefusco, A.: La bleumetilenereazione nelle malattie infettive. Gior. internaz. d. sc. med. Napoli, n. s., 1907, xxix, 460.
15. Ferrari, G.: Sulla bleumetilenereazione. Gazz. d. osp. Milano, 1907, xxviii, 533.

He also claimed that the reaction was not affected by glucose, indican, creatinin and acetone.

Lambrior[16] found the reaction to be irregular in typhoid fever, as it did not appear in some cases, and in others was alternately negative and positive on different days. He also had positive reactions in many other diseases, but in pleurisies, it was only present in the tuberculous variety. He concluded with Zatzomir[17] that it was of no clinical value.

Seuffert[18] emphasizes the difficulty in discriminating between greens and greenish-blues. Using Russo's method in a large series of cases of tuberculosis, he obtained positive reactions in many cases, but he does not consider it of much absolute value. In another large series of various diseases, not including typhoid fever, a negative reaction was always present.

Rolleston[19] found the methylene-blue reaction positive in forty-four out of fifty-four cases of typhoid fever, using the method of Russo. Of the ten negative cases, eight were convalescent and two were very mild cases. Positive reactions were obtained occasionally in lobar pneumonia, bronchopneumonia and scarlet fever. In a large variety of diseases, the reaction was constantly negative. He regarded it as an excellent indicator of a relapse, and also claimed that its disappearance during the course of an attack was due to a lack of function of the kidney. The filtration of the urine to remove phosphates and urates is advised by him. He regarded the test as of marked diagnostic value due to its simplicity and its early appearance, even before the Widal reaction.

Boggs[20] states that "Russo's methylene-blue test has been shown to be absurd and deserves no further notice."

Rolph and Nelson[21] have recently published a report of their researches as performed at the Toronto General Hospital. For a year they employed it as a routine proceeding in the hospital and vouch as to its efficacy as a diagnostic aid in typhoid fever, if applied early in the disease. Of fifteen patients examined, thirteen gave a positive Russo, eight of these gave a positive diazo, and seven a positive Widal. Two

16. Lambrior, A. A.: Note sur la reaction au bleu de methylene en urologie et sa valeur clinique. Bull. soc. d. med. et nat. de Jassy, 1905, xix, 202 and 263.

17. Zatzomir, V. D.: Thesis. La Reaction au bleu de methylene et sa valeur clinique. Jassy, November, 1905.

18. Seuffert, O.: Kritische Untersuchungen uber den Ersatz der Ehrlich'schen Diazoreaktion durch die Russo'sche Methylenblaureaktion. Heidelberg, 1906, J. Horning.

19. Rolleston, J. D.: The methylene blue reaction of Russo in enteric fever. Med. Press and Circ., London, n. s., 1906, lxxxiii, 303; also Transvaal Med. Jour., 1906-7, ii, 268.

20. Boggs, T. R.: Laboratory Methods in the Diagnosis of Typhoid Fever. Old Dominion Jour. Med. and Surg., Richmond, 1908-9, viii, 161.

21. Rolph, F. W., and Nelson, W. H.: Some Experiences with Russo's Typhoid Fever Test. Med. Sentinel, Portland, Ore., 1910, xxx, 449.

cases reacted negatively to all three tests. One of these, however, gave a positive blood culture and had typical symptoms. The other was an unusual case. The method of Russo was employed, and any urine containing bile was discarded, as it gives a green reaction which cannot be distinguished from the positive reaction. They paid especial attention to diseases simulating typhoid fever in their onset, as influenza, endocarditis and slight septic cases, but the reaction was constantly negative. They regard the cause as a reduction process due to the presence of unknown bodies in the urine. They did not find the gradually returning bluish tinge of much assistance in prognosis, as so many of the dangers of typhoid fever are, as it were, accidental, and not due directly to the severity of the infection.

The following has appeared in the literature since the report of Rolph and Nelson, all observers using the method of Russo:

Lemaire[22] agrees with the conclusions of Cousin and Costa, et al, that the test is of no clinical value and that it is simply a physical phenomenon. He also states that it disappears after decolorization with lead acetate and charcoal. Rolph and Nelson's conclusions are not confirmed. Peskova[23] agrees with Lemaire.

Grover[24] does not consider the methylene-blue reaction of value, particularly when compared with the blood-culture. He did not find it positive in all cases of typhoid fever, but found it positive in many non-typhoid cases.

Rankin[25] concludes that the Russo reaction appears positive in typhoid fever, pneumonia, measles and empyema and occasionally in scarlet fever and other diseases, but considers it of some diagnostic value in typhoid fever. He states that it appears more frequently than the diazo reaction, that its intensity indicates the severity of the infection, but disagrees with Rolph and Nelson that it is a good indicator of a relapse or of lysis. It is not pathognomonic of typhoid fever.

Ker[26] (quoting Rankin) thinks unfavorably of the Russo test and considers it inferior to the diazo reaction.

Gambill and Hawley[27] found the Russo reaction positive in eleven cases of typhoid fever and negative in all other cases, except in tuberculosis occasionally. They recommend it because of its early appearance,

22. Lemaire, P.: Reaction de Russo et fievre typhoide. Gaz. hebd. d. sc. méd. de Bordeaux, 1912, xxxiii, 124.

23. Peskova, A.: The Russo Reaction. Med. Obozr., 1911, lxxvi, 155.

24. Grover, A. L.: The Value of Russo's Typhoid Fever Test. Boston Med. and Surg. Jour., 1912, clxvi, 706.

25. Rankin, T. T.: Russo's Methylene-Blue Reaction. Hospital, London, 1911-1912, li, 87.

26. Ker: Manual of Infec. Dis., 1910.

27. Gambill, W. H., and Hawley, M. C.: Russo Reaction in Typhoid Fever. Illinois Med. Jour., Springfield, 1912, xxi, 592.

before the Widal or diazo reactions, its appearance in some cases in which the Widal and the diazo reactions are never positive, and on account of its simplicity. Drugs had no effect, nor had boiling sufficient to coagulate albumin. Their cases occurred in an epidemic in the Watertown State Hospital, and they were able to eliminate many cases by this simple test, while a blood examination in so many cases would have been no light task.

Hager[28] (quoting Gambill and Hawley) considers the methylene-blue reaction more accurate than the diazo reaction, and states that the color disappears on prolonged boiling.

AS A CONFIRMATORY TEST

Williams[29] concludes that the Russo reaction is valuable, especially when used in conjunction with the Widal and diazo reactions. Deductions from the use of all three, he claims, will clear up many misty diagnoses. He advises the use of all three every five days during the course of the disease. His table of conclusions is appended below.

Bouchot, Bovier and Malespine[30] found the reaction positive in fifteen out of seventeen cases of typhoid fever, in two out of three relapses, and consider it to be of good diagnostic value, except that it is occasionally found in other diseases, as measles, erysipelas, salpingitis, pulmonary tuberculosis, acute gastric indigestion, tubercular meningitis and pneumonia. It is not due to albumin nor urates, nor to the fever, as it was negative in many febrile cases. Its appearance in such diseases as pneumonia, erysipelas, measles and small-pox does not materially lessen its clinical value, as the clinical signs of these conditions are sufficient to make a differential diagnosis. Its appearance in tuberculosis and acute gastric indigestion is, however, not favorable. They state that the positive reaction is present in practically every case of typhoid fever, appearing usually as early as the second or third day.

Wallis[31] concludes, after observation in many different diseases, that it is very valuable in the diagnosis of typhoid fever, and is more reliable than the diazo reaction. He advises the use of a control of normal urine and emphasizes the difficulty of detecting the proper color, at first. He agrees with Russo as to its prognostic import. It was found occasionally in measles, small-pox, chronic and suppurative tuberculosis. He never found it positive in acute miliary tuberculosis, and therefore considers it of special value in differentiating that condition from typhoid fever.

28. Hager: Zentralbl. f. inn. Med., 1905, p. 1100.

29. Williams, B. G. R.: The Widal, Diazo and Russo Reactions in Typhoid Fever—An Interdependence. Arch. Diag., 1912, v, 53.

30. Bouchot, Bovier and Malespine: Valeur diagnostique de la reaction de Russo dans la fievre typhoide. Lyon méd., 1912, cxix, 103.

31. Wallis, R. L. M.: Methylene-Blue Test for Typhoid Fever. St. Barth. Hosp. Jour., 1912, xix, 134.

AUTHOR'S MODIFICATION

It is not the purpose of this paper to discuss the value of the diazo reaction of Ehrlich, nor to compare it with the Russo methylene-blue reaction. However, as most of the foregoing authors have made a com-

TABLE 1.—OCCURRENCE OF REACTIONS IN TYPHOID FEVER.

	Widal	Diazo.	Russo
Appears when?	Appears in typhoid fever usually after first week.	Appears early in typhoid fever.	Appears early in typhoid fever.
Relapse and complications.	Relapses and complications appear to have no effect on the reaction.	Reappears with relapses, but not with complications.	A positive reaction which grows in intensity probably indicates a grave or fatal issue.
Is the technic difficult?	Several methods. Some difficult, others fairly simple.	Technic simple.	Technic exceedingly simple.
Reaction time?	Observation of from 2 to 24 hours necessary.	Technic rapidly completed.	Technic rapidly completed.
Acute miliary tuberculosis?	Never present in this disease.	May appear in this disease.	Perhaps never present.
Always present in typhoid?	No.	No.	No.
In measles?	No.	Sometimes.	No.
In pneumonia?	No.	Sometimes.	?
In malaria?	No.	Sometimes.	No.
In small-pox?	No.	No.	Yes.
Chronic tuberculosis?	No.	Yes, often occurs late in fatal cases.	Yes.
Effect of drugs taken internally?	None.	It is probable that no drug taken internally gives the true diazo reaction, although the differentiation of these pseudoreactions may require some skill. Certain of these drugs may interfere with the positive test.	The positive reaction seems to be given by several drugs, notably hexamethylenamin.
Reaction late in typhoid?	The rule.	The diazo test which makes its first appearance after the second week, points to miliary tuberculosis. When a positive reaction suddenly appears during convalescence, a relapse is expected.	?
Persistent reaction in typhoid?	Gives no prognostic or diagnostic information.	May persist throughout infection without any special significance.	Persistent reaction probably spells a bad prognosis.

parative study of the two, a few facts might be stated in passing. The diagnostic and clinical value of the diazo reaction of Ehrlich is considered superior to the methylene-blue reaction of Russo by all of the authors quoted above except Seuffert, Wallis, Hager, Rankin, Rolleston and Rolph and Nelson, who consider them of equal value. Seuffert points

out particularly the difficulty of properly reading the results of a diazo reaction. He states that it often becomes a matter of personal judgment. Rolph and Nelson, Wallis, Hager and Rankin even place the value of the methylene-blue reaction above that of the diazo reaction. Several of the observers, working with thoroughly decolorized urines, obtained negative diazo reactions in urines which had been positive before decolorization.

The facts published by Rolph and Nelson apparently give a clinical value to this reaction which has been previously overlooked. Stimulated by this very successful report, the reaction was instituted in the Georgetown University Hospital, using the method of Russo. Shortly after this, Dr. Behrend suggested that larger quantities of both the urine and reagent should be used. Acting on this suggestion, a modification and, if possible, simplification of the original technic was attempted, and a satisfactory one was evolved. This modification has been used at the Georgetown University Hospital, the Garfield Memorial Hospital and in many private cases. In all, over twenty-five hundred specimens of urine have been examined, in about one thousand different cases. During the time of these observations, all specimens coming to the laboratories were used, no discrimination being made. Special attention was given to diseases simulating typhoid fever and to all septic cases.

TECHNIC

The modified technic, as used in this series, is as follows:

Make an aqueous solution of methylene-blue of such concentration that when thoroughly mixed, it will just be translucent. Using the ordinary test-tube, use a sufficient quantity of the methylene-blue solution to fill the test-tube just above the bowl. Then fill the test-tube with urine, and after thoroughly mixing, examine against a good daylight and note the color reaction. Emerald or mint green indicates a positive reaction, while any tinge of blue renders it negative.

The modified technic is advantageous because it simplifies the preparation of the reagent, it obviates the necessity of using exact quantities, and especially it gives a larger quantity of fluid by which the correct color may be judged. It might be added that the solution of methylene-blue keeps indefinitely without apparently undergoing any changes.

It is a fact, not to be disputed, that the correct reading of a color reaction is a very difficult matter in most instances, and in many becomes a matter of personal interpretation. The differentiation of greens from greenish-blues and some light blues very frequently becomes difficult. This difficulty was experienced in making these tests, and although appearing very simple in actually making the reaction, the proper interpretation, nevertheless, becomes a matter of experience. An ability accurately to distinguish colors is, of course, essential. The whole

procedure is facilitated by the use of a larger quantity of fluid, and by the use of a control in the beginning. The latter can readily be made by using a bile-containing urine which produces a clear emerald green. Too much emphasis cannot be laid on this color differentiation, as it is probably in this particular that many of the earlier observers were in error. When only 5 c.c. of the combined fluids are used, it is practically an impossibility properly to divide a series of colors that so closely simulate each other. The color to be obtained is an absolutely clear emerald or mint green, the slightest tinge of blue immediately indicating a negative reaction. It is in this detail of the test that a perfect judgment of colors, gained by experience and the use of a control, is absolutely essential. Closely observing these precautions, a number of dark urines were diluted and light urines were concentrated, and in no instance did a previously positive urine become negative, or *vice versa*.

Certain urines must be eliminated in testing for this reaction, as they produce a green which is of no clinical importance. As stated by Rolph and Nelson, those containing bile must be discarded, and as noted in this series, those containing blood must also be discarded. Urines rendered cloudy by phosphates, urates, etc., should be filtered.

RESULTS WITH MODIFIED RUSSO REACTION

In this series of one thousand different cases, the only diseases showing a constant positive reaction were typhoid fever and malaria. A few positive reactions were obtained in other diseases, but these were not very numerous.

There were forty-six cases of typhoid fever examined, in which forty-one gave a positive methylene-blue reaction. Of the five negative cases, the temperature in one had been normal for five days and in another it had been normal for two days. The urine of the third patient was neutral in reaction, and after acidification with acetic acid, a positive reaction appeared. This same case showed a positive reaction later when a relapse occurred. Of the other two negative cases, one was a very mild one. Of the forty-one positive cases, two never showed a positive Widal reaction, twelve did not show a positive Widal until a number of days after the appearance of the methylene-blue reaction, and twenty-nine were positive to both tests. In the last-mentioned twenty-nine cases, one had an intercurrent lobar pneumonia with failure of resolution and another was complicated by bronchopneumonia. Still another was a case of pulmonary tuberculosis with an intercurrent typhoid infection. Russo's observation regarding the gradual return of the bluish tinge during convalescence was confirmed. Its prognostic value is to be doubted, for, as stated by Rolph and Nelson, the dangers of typhoid fever are due in the greater part to accidents. It does, however, emphasize

the necessity of using the test early in the disease, as it usually appears in the first two or three days of the disease. Its constant reappearance in relapses in the above cases, gives it some value in this respect.

Of nine cases of malaria, seven of the tertian and two of the estivo-autumnal types, all gave a positive reaction. However, a negative reaction was quickly obtained on the fall of temperature after treatment with quinin. The fact that a positive reaction is found constantly in typhoid fever and malaria does not seem to lessen its clinical value, as a differentiation is usually easily made by the clinical signs and symptoms, the blood examination and the therapeutic test.

The other diseases examined in this series, and in which a negative reaction was obtained, except in a few cases, are endocarditis, influenza, interstitial and parenchymatous nephritis, localized and diffuse peritonitis, tuberculous peritonitis, acute gonorrheal urethritis, gonorrheal arthritis, post-operative fever, slight and severe septic fevers, septicemia, pulmonary tuberculosis, tuberculous adenitis, tuberculous osteomyelitis, lobar and lobular pneumonia, erysipelas, measles, scarlet fever, chicken-pox, mumps, syphilis, sarcoma, carcinoma, benign tumors, gastric ulcer, gastritis, gastro-enteric intoxication, anemia, acute articular rheumatism, phlebitis, gangrene, exophthalmic goiter, diabetes, cystitis, tonsillitis, bronchitis, abortion, pregnancy, cirrhosis of the liver, appendicitis, and in many healthy individuals, a number of whom had received the course of typhoid prophylactic vaccination.

A few positive results were obtained in the above, namely, one case of acute articular rheumatism, two cases of lobar pneumonia, one case of pregnancy which was afebrile, two cases of abortion which were afebrile, one case of post-operative fever, two cases of acute pneumonic tuberculosis, one case with an irregular fever, in which the Widal was negative, in which no blood-culture was made and in which no definite diagnosis was made, and one case of cirrhosis of the liver. Other cases of these same diseases were carefully examined, but at no time was a positive reaction present, except in the above noted instances.

RECAPITULATION

The following facts are stated above, but to recapitulate for a moment. Many observers state that decolorization changes a positive to a negative reaction, and likewise others state that it affects the diazo similarly. Furthermore, surely such strenuous decolorization as with lead acetate and charcoal must cause some chemical changes. The statement that all dark or concentrated urines give positive results is incorrect, as observed in this series, using larger quantities of fluid. The concentration of light urines and the dilution of dark urines did not change the reaction previously obtained.

The opinions of the different observers regarding this test seem to have run almost the complete gamut. On one hand a small minority attach considerable clinical importance to it, while on the other hand, a large majority relegate it to the scrap heap as worthless. Very few have taken the middle ground, as in this paper, regarding this test simply as one link in the chain of evidence, the object of which is to make a correct diagnosis. Very few laboratory tests are absolutely pathognomonic of a specific disease, this one being no exception, and likewise a diagnosis is seldom, if ever, made on a single symptom or test. It is simply by the ability to obtain all the facts bearing on the case that logical conclusions are reached, and a correct diagnosis made. Williams[32] very aptly states that many tests are of no avail because they are not properly interpreted. He points out that in bacteriological work, it is the positive results that are valuable, as finding the tubercle bacillus in the sputum. I quote him below regarding the chemical reactions:

> It is the negative chemical reaction which is of the most value. A urine, which on repeated tests, fails to show serum albumin, probably is not secreted by an inflamed kidney, and the physician is thus spurred on to search for further cause of the trouble.
>
> With these limitations in mind, we have recourse to a host of valuable short cuts when approaching a case difficult of diagnosis. For example, here is a patient with a fever probably caused by the typhoid bacillus; but the Widal reaction is as yet negative, and a diagnosis cannot be made without further evidence. Holding in mind this patient, let us consider for a moment the chemical urinary test devised by M. Russo. This is a simple little reaction which may be applied by any physician with a test-tube, some methylene-blue and two minutes' time; and the technic of which is repeated so frequently in current medical literature that I have not thought best to give it space here. The lazy physician hoped that the positive reaction would enable him to diagnosticate all his cases without having to study his patients, and as soon as he was disappointed, he condemned the test in no uncertain language. It is not to be denied that the positive reaction is found elsewhere than in enteric fever, but recalling that it is the negative reaction in clinical chemistry which aids us must, suppose we apply it to the patient mentioned above, hoping that it may serve us as a short cut.
>
> The test is negative. What is our conclusion? If this patient has a fever, this is probably not caused by the typhoid bacillus, and we may as well set about searching elsewhere for the cause of the trouble. Of course, such a presumption is not fair unless the test is repeated at frequent intervals. I have seen this test in its negative phase direct the physician to an abscess of the gall-bladder and in another case to a pyelitis.

SUMMARY

1. The constant positive reaction in typhoid fever and its rare appearance in other conditions, gives this test marked corroborative value. A negative reaction is very good evidence that the condition is not typhoid fever.

32. Williams, B. G. R.: Some Short Cuts to Diagnosis. Med. Times, December, 1912, p. 361.

2. Its prognostic value is to be doubted, but its continued appearance in severe cases, and reappearance in relapses is important.

3. Its simplicity strongly recommends it, with certain limitations, to wit, that a differentiation of the true greens from the bluish-greens is a matter of practice and experience.

4. Its very early appearance will aid in isolating a suspected patient at once, and general prophylactic measures will be instituted.

5. The success met with in this series with the modified technic should insure a complete investigation for this reaction.

BOOK REVIEW

AN INTRODUCTION TO THE STUDY OF INFECTION AND IMMUNITY. INCLUDING SERUM THERAPY, VACCINE THERAPY, CHEMOTHERAPY AND SERUM DIAGNOSIS. By Charles E. Simon, M.D., Professor of Clinical Pathology and Experimental Medicine, College of Physicians and Surgeons, Baltimore. Octavo, 301 pages; illustrated. Cloth, $3.25, net. Lea & Febiger, Philadelphia, 1912.

The immense and rapidly increasing literature on the subjects considered in this book, the novelty of many of the discoveries and the complexity of terminology make commendable efforts at a connected account of the present situation. From his own participation in the subject and his success as a bookmaker, the author of this work was justified in undertaking it. On the whole, he may be congratulated on his success. He has given a fairly adequate view of the theory and practice of the subject. It is especially true of the more "practical" chapters, for in the introductory part the author indulges in a fancy for splitting hairs and for *obiter dicta*. Thus, it seems unnecessary to exalt immunity studies by emphasizing the imperfection of previous knowledge. The folly of such a course is well illustrated when, after the trite and overworked emphasis on the imperfections of art, the author grudgingly admits that it is a debatable point whether the means at Nature's commands are, after all, perfect. He might get some suggestions from a recent paper by Maverick (*Med. Rec.*, Oct. 12, 1912). As the latter says, "What does Nature do for the patient in the stupor of typhoid, with renal calculus, ulcer of the pylorus, a torn cervix, high blood-pressure?" We doubt if it is true, and feel sure that the author cannot prove, that "typhoid fever patients always still pursue the same course which was so well described by the physicians of the middle ages." We are not sure where the author finds his references, but believe that while some medieval physicians, like Nathan Smith at a later period, cared well for their patients, those of to-day pursue a much better course than they did fifty or a hundred years ago.

A similar obscurity surrounds the author's discussion of infection, which has no advantages over the current ideas among thoughtful writers. The same tendency is shown in the discussion of virulence, though in this the practical relations of virulence, the effects of passage through animals and capsule formation are admirably described.

The most important discoveries in immunology are well and clearly described so that the various theories, the terminologies and the important phenomena, like anaphylaxis, active and passive immunity and chemotherapy, are adequately presented.

The most useful preventive and therapeutic methods are well described; chemotherapy is sufficiently described in connection with salvarsan, and the work closes with a clear description of diagnostic methods including the Widal, Wassermann, tuberculin and luetin tests. It will prove a useful guide to physicians, and a convenient reference for advanced workers who are not able to obtain first hand information on all the problems discussed.